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TELLURIUM BASED SYNTHETIC METHODOLOGY AND SYNTHETIC STUDIES RELATED TO MEVINOLIN AND COMPACTIN

University — Université

UNIVERSITY OF ALBERTA

Degree for which thesis was presented — Grade pour lequel cette thèse fut présentée

Ph. D.

Year this degree conferred — Année d'obtention de ce grade	Name of Supervisor — Nom du directeur de thèse
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TELLURIUM BASED SYNTHETIC METHODOLOGY
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SYNTHETIC STUDIES RELATED TO MEVINOLIN AND COMPACTIN

by

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A THESIS

SUBMITTED TO THE FACULTY OF GRADUATE STUDIES AND RESEARCH

IN PARTIAL FULFILMENT OF THE REQUIREMENTS FOR THE DEGREE

OF DOCTOR OF PHILOSOPHY

DEPARTMENT OF CHEMISTRY

EDMONTON, ALBERTA

SPRING 1984

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Supervisor

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External Examiner

Date December 21, 1983

FOR MY FAMILY

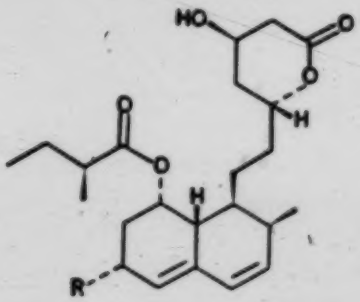
Abstract

This thesis deals with two subjects: tellurium based synthetic methodology and synthetic studies related to Mevinolin and Compactin.

The first chapter describes a new method for coupling allylic halides based on tellurium chemistry. A variety of allylic bromides and chlorides were treated with Te^{2-} (generated *in situ* from tellurium powder) to afford 1,5-dienes. The average yield was 78% over 11 examples. Mechanistic studies suggest that bisallylic tellurides are produced, and that these thermally decompose into allylic radicals which then dimerize.

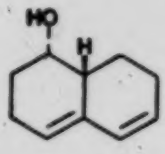
The first chapter also contains a review of the applications of tellurium reagents in organic synthesis, and a survey of other methods for coupling allylic halides.

The second chapter of this thesis describes synthetic studies related to the fungal metabolites Mevinolin (**1**) and Compactin (**2**).



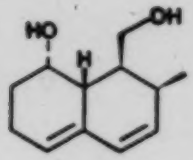
1 R=CH_3
2 R=H

In model experiments, the hexahydronaphthalen-1-ol **103b** was prepared by a process based on aldol methodology and titanium induced intramolecular carbonyl coupling.

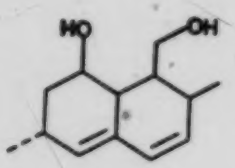


103b

The same approach was then used to prepare the diols **127b** (in racemic form) and **138** (as a mixture of diastereoisomers). These substances represent the hexahydronaphthalene portions of Compactin and Mevinolin, respectively.



127b



138

Model studies on the coupling of these bicyclic units to a suitable lactone portion are also discussed including a promising route based on an unusual Wittig reaction.

In addition to describing our own synthetic work, the second chapter reviews the published synthetic achievements of other researchers in this field.

Acknowledgements

I would like to express my sincere gratitude to Dr. D.L.J. Clive for his constant guidance and encouragement during the course of my studies, and for his interest and assistance in the preparation of this thesis.

My gratitude also extends to the Natural Sciences and Engineering Research Council of Canada, and the Alberta Heritage Foundation for Medical Research, for financial support.

The assistance of Dr. T. Nakashima, Mr. G. Bigam and Mr. T. Brisbane in the use of high field NMR spectrometers is gratefully acknowledged.

Finally, I would like to thank the many members of our research group and others in this department who have made my studies here a most enjoyable experience. Special thanks go to Dr. M. Majewski and Miss S. Bennett for their assistance during the preparation of this manuscript and to Mrs. Lu Ziola for typing this thesis.

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CHAPTER 1

ORGANIC TELLURIUM CHEMISTRY:
THE COUPLING OF ALLYLIC HALIDES WITH Te^{2-}

I. INTRODUCTION

By its nature, synthetic organic chemistry requires a large array of reagents and reactions for the controlled manipulation of organic compounds. As chemists attempt to achieve the total synthesis of increasingly complex and sensitive molecules, they look to relatively unexplored regions of the periodic table as possible sources of new reagents with which to carry out hitherto unknown transformations, or classical processes in milder or more selective ways. For example, recent years have seen an explosive growth in the use of organic selenium chemistry in synthesis.[1] By contrast, the exploration of organic tellurium chemistry in this respect is still at an early stage.

A. Tellurium Reagents in Organic Synthesis

The element tellurium was discovered in 1783 and was named in 1798.[2] The first organic derivatives of tellurium were prepared as early as 1840.[3] Since that time, a considerable number of publications has appeared on the general subject of tellurium in organic chemistry,[2] however, only a very limited number of examples exist of the applications of tellurium to transformations not readily accomplished by classical means.

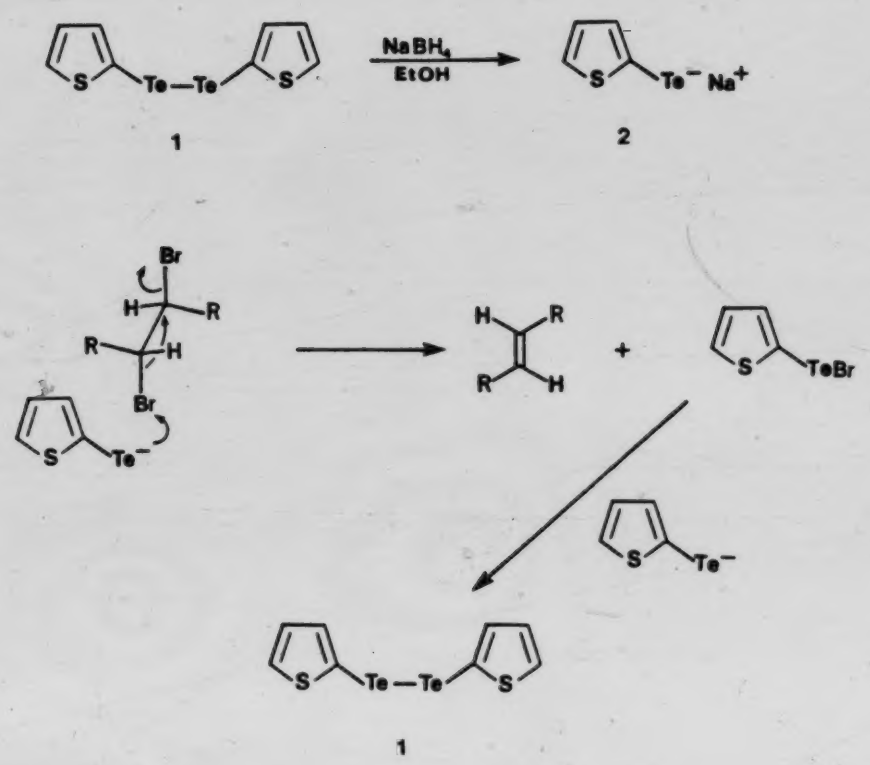
Tellurium Based Reducing Agents. One of the first reports of the use of a tellurium compound as a reagent in organic synthesis involved the application of a diaryl telluride for debromination of vicinal dibromides (eq. 1).[4] Since that time a number of other tellurium reagents have been described which also carry out the same transformation.

$$Ar_2Te + RCH(Br)-CHR'(Br) \longrightarrow RCH{=}CHR' + Ar_2TeBr_2 \qquad (1)$$

These include Ar_4Te_2,[5] NaHTe[6] (which can be prepared *in situ* from Te and $NaBH_4$), and sodium 2-thiophenetelluroate (**2**).[7] The latter is a particularly interesting reagent. Yields are good and the elimination proceeds at, or below, room temperature with a high degree of anti-stereospecificity. The reaction is thought to occur by the pathway shown in Scheme 1.

The telluride reagent **2** is prepared *in situ* by sodium borohydride reduction of bis(2-thiehyl)ditelluride (**1**). Since ditelluride **1** is also a product, the reaction has been

Scheme 1

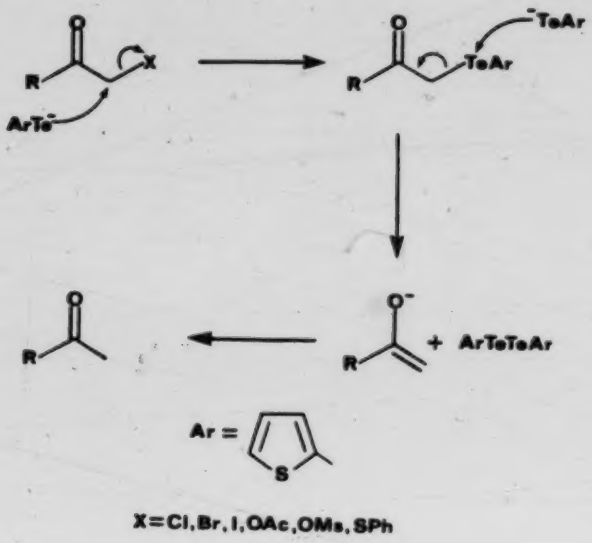


refined to a cycle which is catalytic with respect to **1**. Furthermore, the reaction is self indicating since ditelluride **1** is dark red whereas telluride **2** is colourless. The reaction is performed by mixing a catalytic amount of ditelluride **1** (3-9 mole %) with the vicinal dibromide in ethanol under an inert atmosphere. A solution of $NaBH_4$ in aqueous base is added until the red colour is discharged. At this point the reaction is complete, air is introduced to oxidize the telluride anion **2** back to ditelluride **1**, and the products are isolated.

This reagent has also been used in a similar catalytic fashion to dehalogenate α-chloro, -bromo, and -iodo-ketones and carboxylic acids.[1] In this case, it is apparent that sodium borohydride must preferentially reduce the tellurium-tellurium bond of **1** rather than the ketone carbonyl since halohydrin formation is not observed. The corresponding lithium salt of **2** has been used stoichiometrically (2 equivalents) in dry THF to reduce α-halo, -acetoxy, -mesyloxy and -phenylthio ketones to ketones. The mechanism

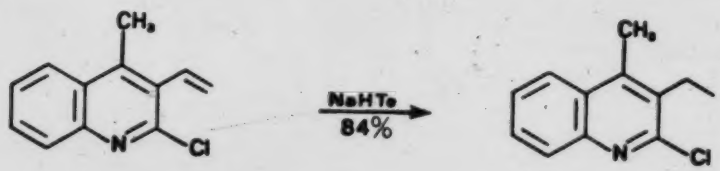
proposed for such transformations is shown in Scheme 2. In some cases, for example, the reduction of tertiary α-haloketones, direct attack of the telluride anion on the halogen may be involved.

Scheme 2



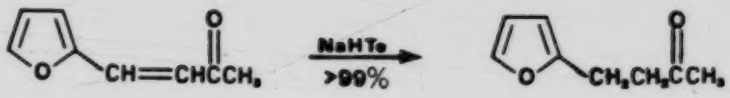
A number of other tellurium reagents have been used for dehalogenating α-halocarbonyl compounds. These include NaHTe,[9] Na_2Te,[10] Na_2Te_2,[10] and sodium *O,O*-diethyl phosphorotelluroate (**4**).[11]

Tellurium reagents have been employed for a variety of other reduction processes. Sodium hydrogen telluride (generated *in situ* from Te and $NaBH_4$) was found to reduce carbon-carbon double bonds in the presence of a variety of functional groups (equ. 2-6).[12,13]



(2)[13]

$$PhCH{=}CHCHO \xrightarrow[>99\%]{NaHTe} PhCH_2CH_2CHO \qquad (3)^{13}$$



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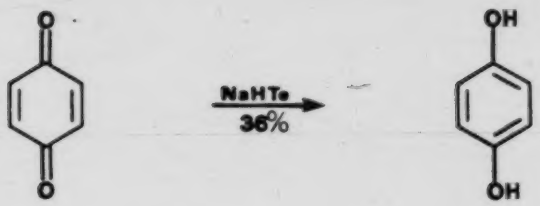

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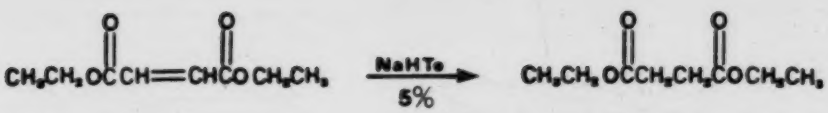
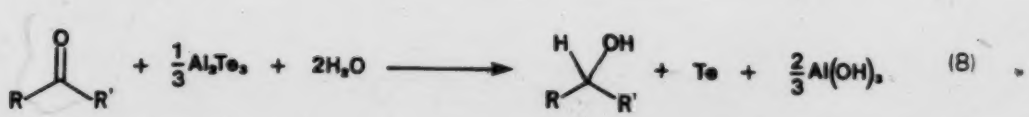


(6)[13]

Hydrogen telluride will reduce benzaldehyde at 0°C under nitrogen (equation 7), however, the toxicity of the reagent, its thermal instability and its sensitivity to air and light make it inconvenient to use.[14]

$$PhCHO + H_2Te \xrightarrow{N_2,\ 0^\circ C} PhCH_2OH + Te \qquad (7)$$

The compound can however be generated *in situ* from aluminum telluride and water, according to equation 8.[14]



(8)

Using this procedure, benzaldehyde was reduced quantitatively whereas *n*-octanal and cyclohexanone gave only 50% and 51% yields of the corresponding alcohols.[14] The reagent selectively reduces the carbon-carbon double bond of α,β-unsaturated carbonyl compounds. No allylic alcohols are obtained. By replacing water in the reaction with D_2O, deuteration can be accomplished. Hydrogen telluride has also been used to reduce a number of other functional groups.[15] Aromatic nitro-compounds and aromatic hydroxylamines give amines while aromatic nitroso-, azo-, and azoxy- compounds are reduced to mixtures of aromatic amines and *N,N'*-diaryl hydrazines, with the latter as the main products (eq. 9-13).

$$PhNO_2 \xrightarrow[THF,\ N_2]{Al_2Te_3,\ H_2O} \underset{90\%}{PhNH_2} \qquad (9)$$

$$PhNHOH \xrightarrow[THF,\ N_2]{Al_2Te_3,\ H_2O} \underset{98\%}{PhNH_2} + \underset{1\%}{PhNHNHPh} \qquad (10)$$

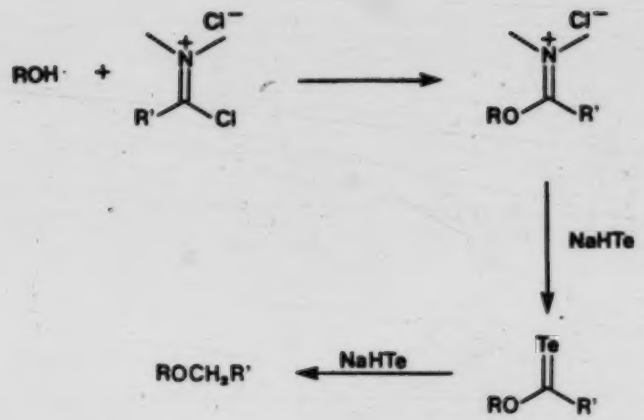
$$PhNO \xrightarrow[THF,\ N_2]{Al_2Te_3,\ H_2O} \underset{16\%}{PhNH_2} + \underset{63\%}{PhNHNHPh} \qquad (11)$$

$$PhN{=}NPh \xrightarrow[THF,\ N_2]{Al_2Te_3,\ H_2O} \underset{4\%}{PhNH_2} + \underset{96\%}{PhNHNHPh} \qquad (12)$$

$$PhN{=}\overset{O}{N}Ph \xrightarrow[THF,\ N_2]{Al_2Te_3,\ H_2O} \underset{6\%}{PhNH_2} + \underset{94\%}{PhNHNHPh} \qquad (13)$$

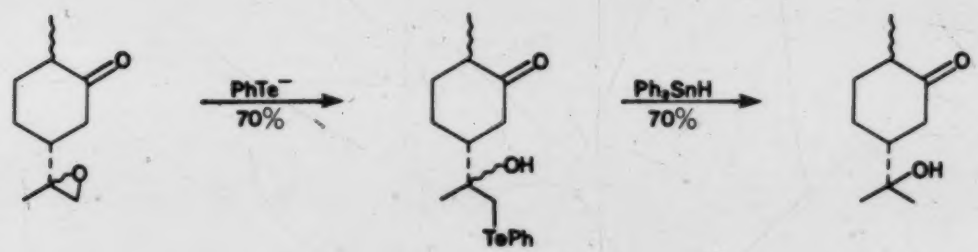
Alcohols have been converted to benzyl and neopentyl ethers using Vilsmeier salts by reduction with sodium hydrogen telluride in a process which was shown to proceed through telluroesters, (Scheme 3), a previously unknown class of compound.[16,17]

Scheme 3



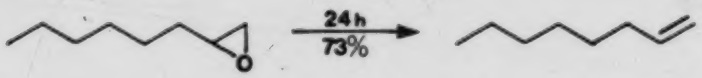
R' = Ph, t-Butyl

Tellurides, which can be prepared in many ways, for example, from alkyl halides or epoxides by nucleophillic displacement using RTe⁻ (generated by $NaBH_4$ reduction of R_2Te_2), can be reduced to the corresponding hydrocarbon with triphenyltin hydride.[11] An interesting example of the utility of this reaction is shown in equation 14. This two step process corresponds overall to reduction of an epoxide in the presence of a ketone, a transformation not easily accomplished by classical means without resorting to protection-deprotection steps.



(14)

Epoxides have been deoxygenated with the reagent sodium *O,O*-diethyl phosphorotelluroate (**4**).[19, 20] This reagent, although extremely air sensitive, can be prepared conveniently *in situ* by reaction of sodium diethylphosphite (**3**) with elemental tellurium. The reagent reacts exothermically with epoxides at room temperature to give alkenes (equations 15-18). Non-terminal epoxides react more slowly than terminal isomers so that selective deoxygenations are possible. Among geometric isomers of disubstituted olefins that with *Z* stereochemistry is more reactive. The deoxygenation is stereospecific: a *Z*-epoxide gives a *Z*-olefin. The reaction works for cyclohexene oxide.



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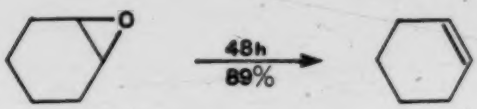

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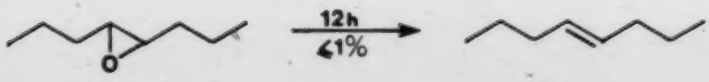

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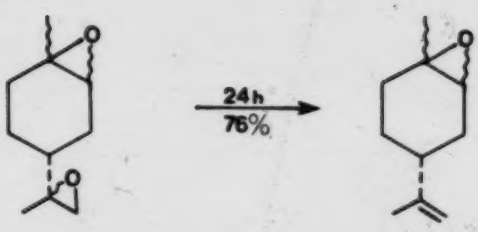
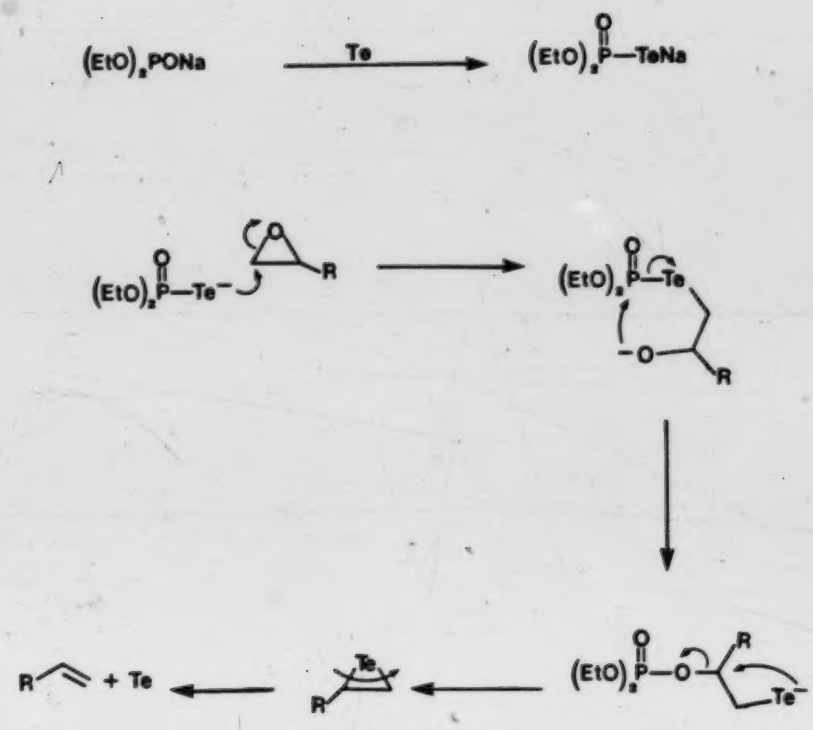


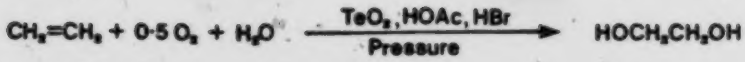
(18)

The mechanism proposed is shown in Scheme 4. Since tellurium metal is produced (Scheme 4) and sodium diethyl phosphite (**3**) reacts faster with tellurium than with epoxides, it is possible to perform the reaction catalytically with respect to tellurium.

Scheme 4

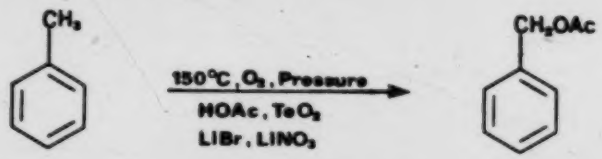


Tellurium Based Oxidizing Agents. A number of tellurium species have been used as oxidants in organic chemistry. Selenium dioxide is a well established oxidizing agent employed in most cases to effect allylic oxidations.[21] Tellurium dioxide, by contrast, has seen limited use and it behaves somewhat differently. Applications of tellurium dioxide as an oxidizing agent were studied as early as 1941,[22] however, the results were not particularly encouraging due for the most part to the low solubility of the compound in almost all organic solvents. More recently, mixtures of tellurium dioxide and acetic acid have found application as catalysts in certain oxidations. For example, ethylene is converted almost quantitatively into ethylene glycol by the process summarized in equation 19.[23,24]



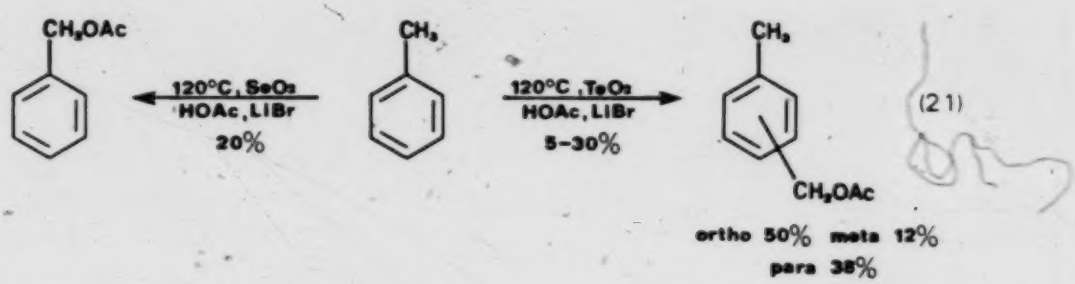
(19)

Similary, alkyl substituted aromatic compounds react at the benzylic position in the presence of pressurized oxygen (equation 20).[23]



(20)

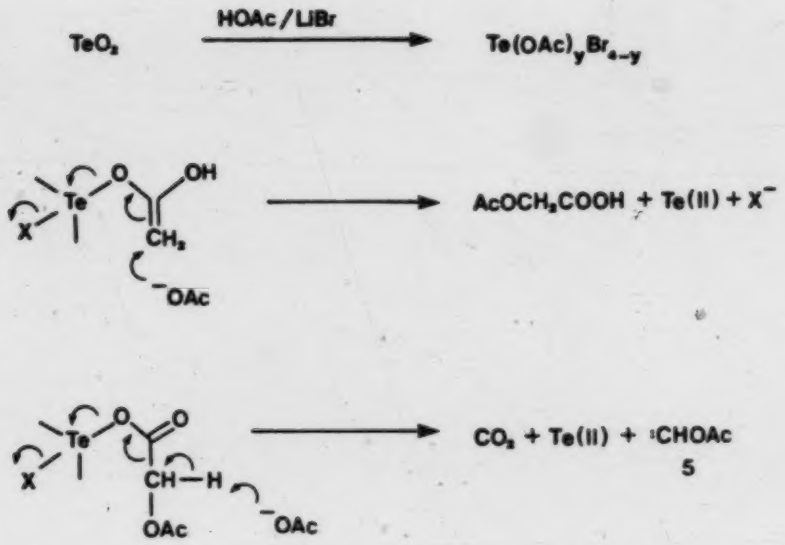
In contrast to this reaction, in the absence of pressurized oxygen, the same reagents give only acetoxymethylation products.[23,24] This result is also in sharp contrast to the behavior of selenium dioxide under the same conditions (equation 21).



(21)

Acetoxymethylation, in the case of tellurium dioxide, is believed to proceed through carbene 5, whose origin is speculated to be as shown in Scheme 5.

Scheme 5

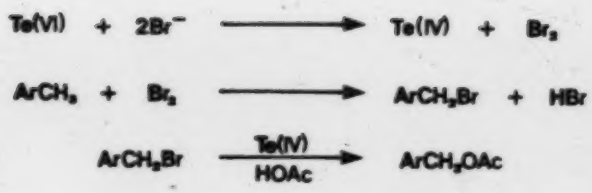


Orthotelluric acid ($Te(OH)_6$) can be used in place of tellurium dioxide , to effect side chain oxidation, according to equation 22.[24]

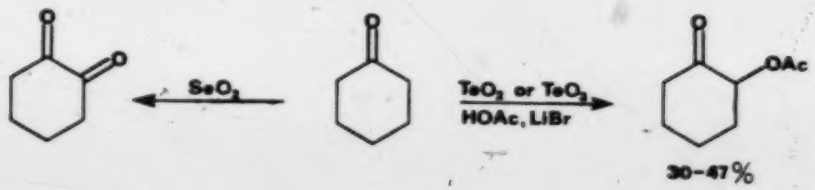
$$ArCH_3 \xrightarrow[LiBr]{Te(OH)_6,\ AcOH} ArCH_2OAc \qquad (22)$$

Lithium bromide is essential and it was found that ring bromination side products are formed. In light of these observations, it was suggested that the benzylic acetates arise by solvolysis of benzylic bromides formed according to Scheme 6. The side chain oxidation observed at high pressures of oxygen with tellurium dioxide (equation 20), may be due to oxidation of a Te(IV) to a Te(VI) species which then reacts as in Scheme 6.

Scheme 6



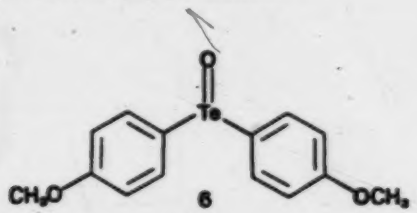
Both tellurium dioxide and tellurium trioxide can be used in acetic acid containing lithium bromide to effect more conventional oxidations. Thus, cyclohexanone is oxidized to α-acetoxycyclohexanone (equation 23).[25] Again this result is in contrast to what occurs with selenium dioxide.[26]



(23)

The tellurium dioxide/lithium bromide/acetic acid/acetic anhydride system has also been used to oxidize butadiene to a mixture of 1,2- and 1,4-diacetoxybutenes.[27]

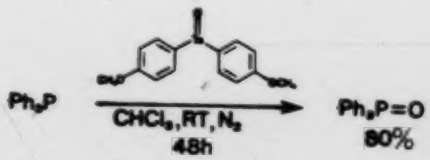
The reagent bis(*p*-methoxyphenyl)telluroxide (6) is a very mild, highly selective oxidizing agent for many synthetic transformations.[28-31]



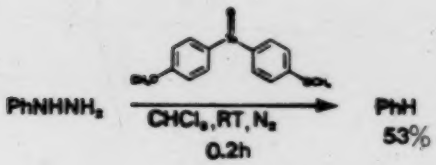
6

It converts phosphines to phosphine oxides, aromatic hydrazines to hydrocarbons,

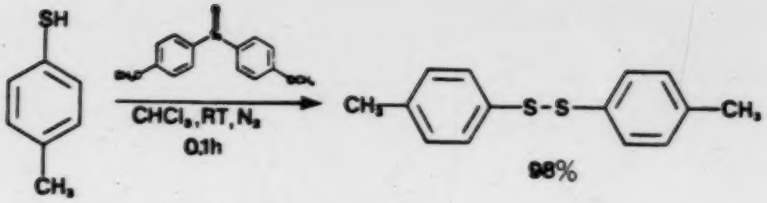
mercaptans to disulfides, and catechols to quinones (equations 24-27). Xanthates, thiocarbonates, thioamides, thiones, and selenocarbonyl compounds are converted to the corresponding oxo derivatives.



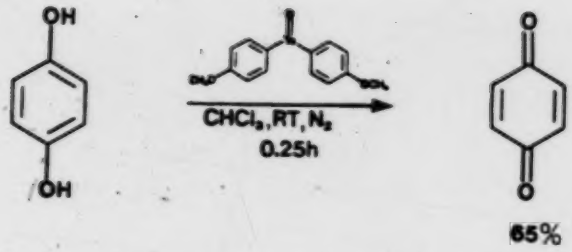
(24)



(25)



(26)

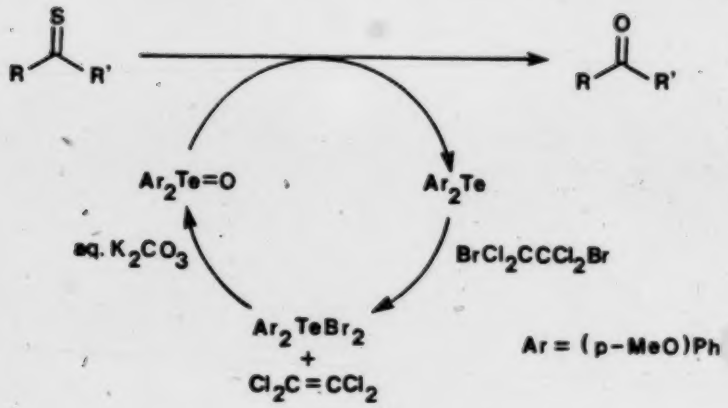


(27)

This reagent will not however oxidize dithiolanes, enamines, aldehydes, ketones, alcohols, pyrroles, indoles, amino acids, aromatic amines, monohydroxyaromatics, esters, hindered thiocarbamates, isonitriles, oximes, aryl hydrazones, sulfides, or selenides.

The reagent has been used catalytically for conversion of thiocarbonyl compounds into the oxo analogues (Scheme 7).[38]

Scheme 7



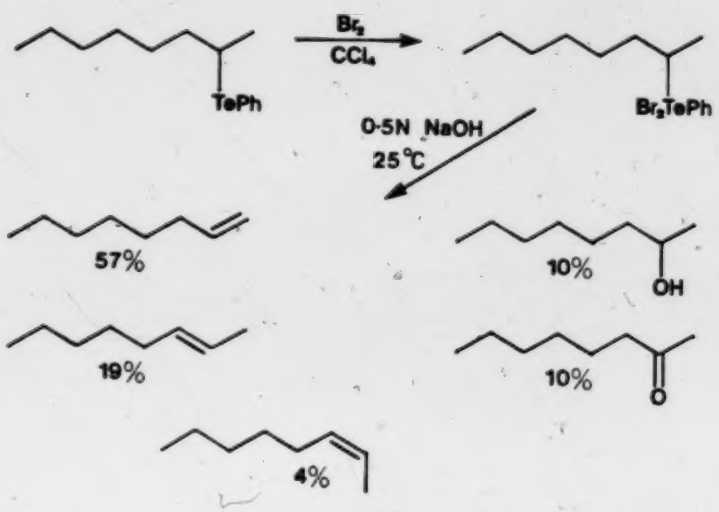
The telluroxide is regenerated in the reaction medium by oxidation to the dibromide using 1,2-dibromo-tetrachloroethane followed by hydrolysis with aqueous base.

The Telluroxide Elimination Reaction. The importance of selenium methodology in organic synthesis is due largely to the selenoxide fragmentation reaction.[1,32] Although discovered ony recently, it has become one of the most extensively studied and widely used of the modern reactions. By contrast, relatively little is known of the corresponding behavior of telluroxides.[33-35] The first reported example of the telluroxide elimination reaction was the oxidation of several tellurides in benzene using *tert*-butylhydroperoxide to give mixtures of olefins and alcohols.[33] The latter were, presumably, the result of a 1,2-shift of the telluroxide or the corresponding tellurium dioxide. Subsequent studies have established that primary alkyl aryl telluroxides require relatively higher temperatures and longer reaction times than the corresponding selenoxides (equation 28).[34]

$$C_nH_{2n}CH_2CH_2\overset{O}{\overset{\|}{}}TeAr \xrightarrow[24\,h]{80^\circ C} C_nH_{2n}CH{=}CH_2 + C_nH_{2n}CH_2CH_2TeAr \qquad (28)$$

Ar = p-CH_3OPh–

Secondary alkyl aryl telluroxides undergo the fragmentation at room temperature to give mixtures of terminal and internal alkenes, together with smaller amounts of alcohols and ketones (equation 29).[33] The alcohols may arise from 1,2-tellura-shifts and the ketones by subsequent oxidation of the alcohols.



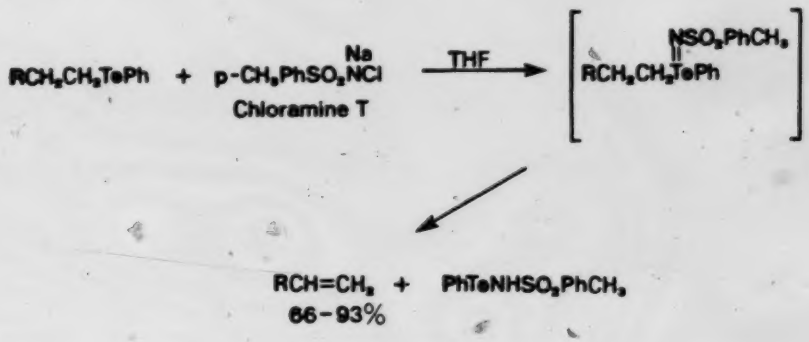
(29)

For linear olefins, the ratio of terminal to internal alkene is higher for the telluroxide fragmentation (*ca.* 2.5:1) than for the corresponding selenoxide (1.6:1) or sulfoxide (1.5:1) reactions.[33]

The telluroxide elimination appears to be a less facile process than the corresponding selenium reaction. The reasons for this may be that all telluroxides were isolated as hydrates which are most certainly dihydroxytelluranes with a four coordinate tellurium atom. This constitution may lower the basicity of the oxygen atoms.[33]

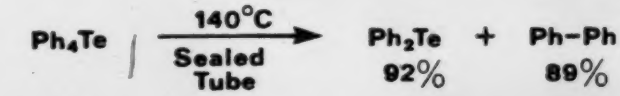
Secondly, longer bond lengths for the carbon-tellurium and tellurium-oxygen bonds may place the oxygen atom further away from an appropriate hydrogen atom.[33,35] The lower reactivity of primary vs. secondary telluroxides may be due to a flow of electrons from carbon to tellurium in the transition state, making carbonium ion stability an important factor.[33]

A different, but related process is the reaction of alkyl phenyl tellurides with chloramine-T (equation 30).[36] With this reaction, one example of a secondary alkyl phenyl telluride gave a mixture of terminal to internal alkenes of 2.2:1.



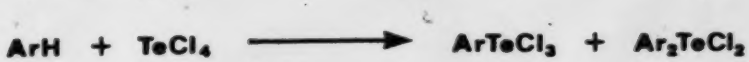
(30)

Tellurium Reagents for Carbon-Carbon Bond Formation. For synthetic organic chemistry, reactions which form carbon-carbon bonds are of primary importance. To this end, tellurium reagents have been used only sparingly. Tetraaryl tellurides decompose upon heating to give diaryl tellurides and coupled aryls (equation 31).[37,38] Mechanistic studies suggest a non-radical, concerted process.



(31)

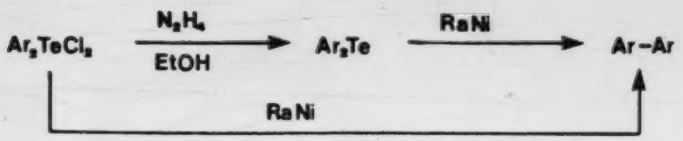
Tellurium tetrachloride acts as an electrophile towards activated aromatic compounds (ArX, X = -OR, -SR, $-NR_2$, etc.) to give aryl tellurium halides (equation 32).



(32)

These can be reduced to diaryl tellurides and/or treated with Raney nickel to generate coupled biaryls (Scheme 8).[39,40] Unactivated aromatic compounds will react with tellurium tetrachloride in the presence of Lewis acids.

Scheme 8



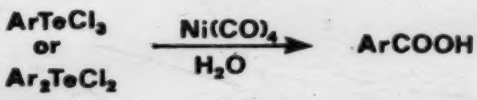
Diaryl tellurium dichlorides can be carbodetellurated by treatment with Pd(II).[41] In the presence of alkenes, olefinated aryl compounds are obtained in moderate to quantitative yields (equation 33).

(33)

R= Ph, CO_2CH_3, CN, CHO, COR, CH_2OH, CH_2OAc, CH_2Br

In the absence of an alkene, coupled aryls are formed. The reaction probably proceeds via a reactive aryl palladium species resulting from Te(IV) to Pd(II) exchange. The reaction can be done catalytically with respect to palladium if an oxidizing agent such as *tert*-butylhydroperoxide or copper(II) chloride is present.

Another carbon-carbon bond forming reaction involving aryl tellurochlorides is carbonylation in the presence of tetracarbonylnickel (equation 34).[42]

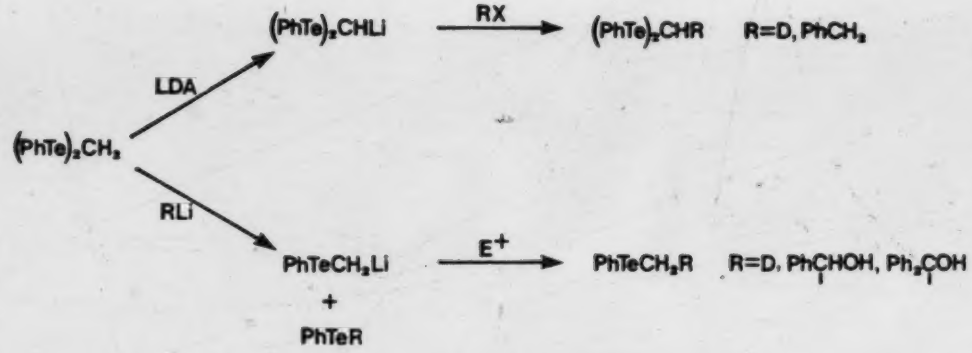


(34)

A number of tellurium stabilized carbanions have been developed. $PhTeCH_2Li$ and $(PhTe)_2CHLi$ have been prepared and trapped by a variety of electrophiles (Scheme 9).[43] These reactions become particularly useful in conjunction with the above mentioned

telluroxide elimination (equation 35) or in conjunction with the reaction of tellurides with halogens (equations 36, 37).[44]

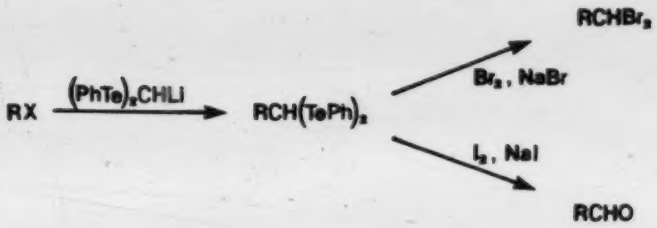
Scheme 9



$$RCH_2X \xrightarrow{PhTeCH_2Li} PhTeCH_2CH_2R \xrightarrow[Elimination]{Telluroxide} RCH{=}CH_2 \qquad (35)$$

$$RX \xrightarrow{(PhTe)_2CHLi} (PhTe)_2CHR \xrightarrow[or\ Br_2,\ I_2]{SOCl_2} PhTeCH_2R \quad (X,X) \qquad (36)$$

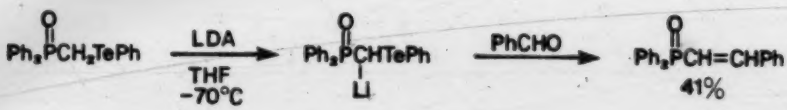
$$PhTeCH_2R \xrightarrow{Heat} RCH_2X + PhTeX_3$$



(37)

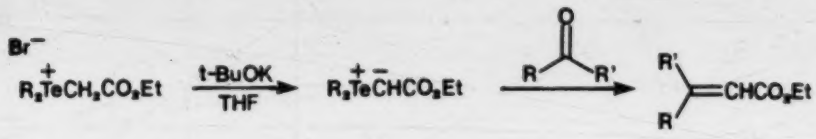
The last reaction (equation 37) shows an example of a tellurium based acyl anion equivalent.

Tellurium stabilized anions have also been used in the olefination of carbonyl compounds (equation 38).[45]



(38)

Several highly stabilized tellurium ylides are known (for example, eq. 39).[46] It is interesting to note that no epoxides are formed in contrast to the corresponding sulfur and selenium reactions.

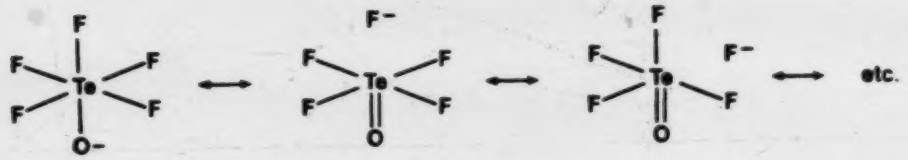


(39)

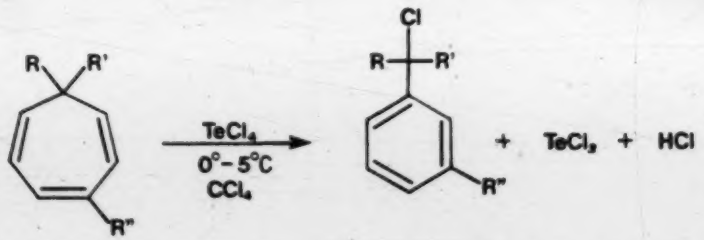
Less is known of tellurium based alkylating agents. One example is $TeF_5(OCH_3)$,[47] which was found to be a stronger alkylating agent than $SO_2(OCH_3)_2$, although weaker than $FSO_2(OCH_3)$. Its alkylating ability is attributed to the formation of the highly stabilized TeF_5O^- ion (Figure 1). $TeF_5(OCH_3)$ was used to methylate DMF, pyridine, and potassium

phthalimide. However, the reagent does have two electrophilic sites, the methyl group and the tellurium atom, so that in some cases, it is possible to observe nucleophilic attack at tellurium.[47]

Figure 1

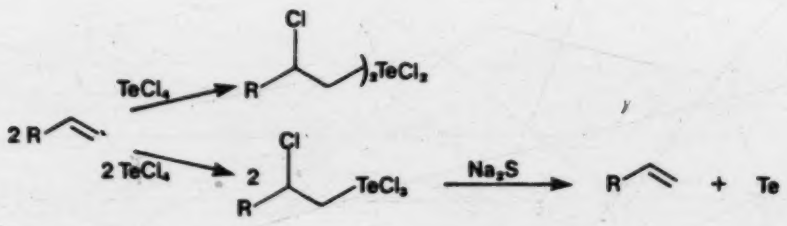


Other Uses of Tellurium in Organic Synthesis. The electrophillicity of tellurium tetrachloride has been exploited in a number of other reactions. Tropyl derivatives rearrange at elevated temperatures or photochemically to benzene derivatives. With tellurium tetrachloride, the reaction proceeds at, or near, 0°C to give benzylic chlorides (equation 40).[41]



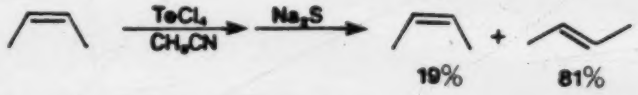
(40)

The reagent also adds to carbon-carbon double bonds (equation 41).



(41)

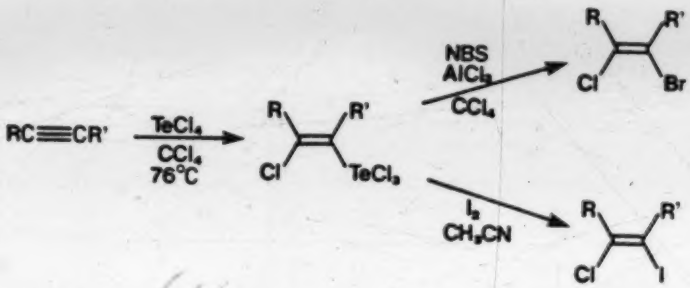
The 1:1 adduct can be reduced cleanly with sodium sulfide back to the alkene and tellurium.[49] This two step sequence is useful as a one pot procedure for inverting the geometry of an olefin (equation 42).



(42)

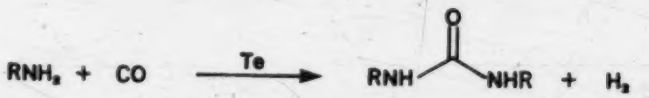
The process is thought to involve predominantly *cis* addition of tellurium tetrachloride across the double bond followed by *trans* reductive elimination. Unfortunately, the stereospecificity of this reaction varies with substrate and solvent, thereby limiting its utility.

Tellurium tetrachloride will add in a *cis* fashion to acetylenes. The intermediate *cis*-chloro-trichlorotellura-olefins react with sources of iodine or bromine to give *cis*-iodo- or bromo-vinyl chlorides (equation 43).[50]



(43)

Finally, tellurium metal has been used as a catalyst in the direct formation of urea derivatives from amines and carbon monoxide (equation 44).[51,52] Formamides are byproducts. Selenium also catalyzes this reaction, but only in the presence of oxygen, and produces water instead of hydrogen.[53]

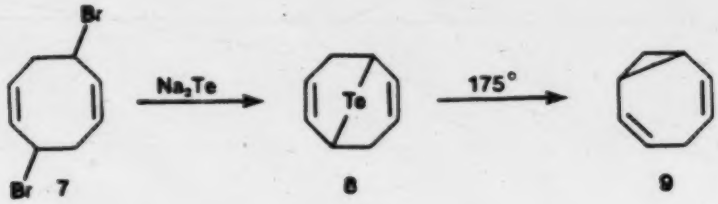


(44)

To summarize, the use of tellurium chemistry in synthetic methodology is still at an early stage of development. The recent and continuing activity in this field shows that

tellurium chemistry is being examined for new and useful reactions, although it remains to be seen whether tellurium will have as significant an impact as selenium on the field of organic synthesis.

Our attention was drawn to this subject by a report that appeared in the literature some time ago.[54] Bisallylic bromide **7**, when treated with sodium telluride in DMF, gave the bicyclic telluride **8**. This compound, upon thermolysis, extruded tellurium and gave hydrocarbon **9** according to equation 45.



7 **8** **9** (45)

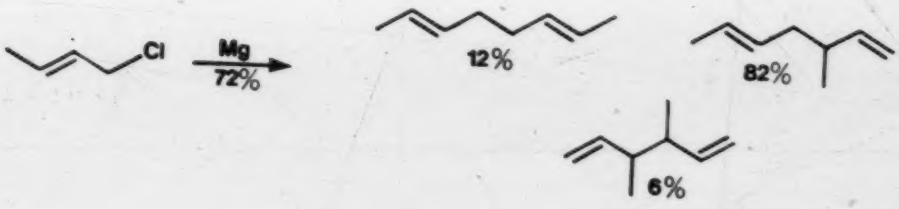
This transformation formally represents an intramolecular coupling of two allylic halides to produce a 1,5-diene. We felt that if the process were found to be a general reaction, it would be possible to exploit the transformation in a synthetically useful fashion. In the event, we were able to develop a new way of forming carbon-carbon bonds in an allylic environment by the coupling of allylic halides.[55] Allylic halides have been coupled by other reagents and these reactions are reviewed briefly in the following section.

B. The Coupling of Allylic Halides

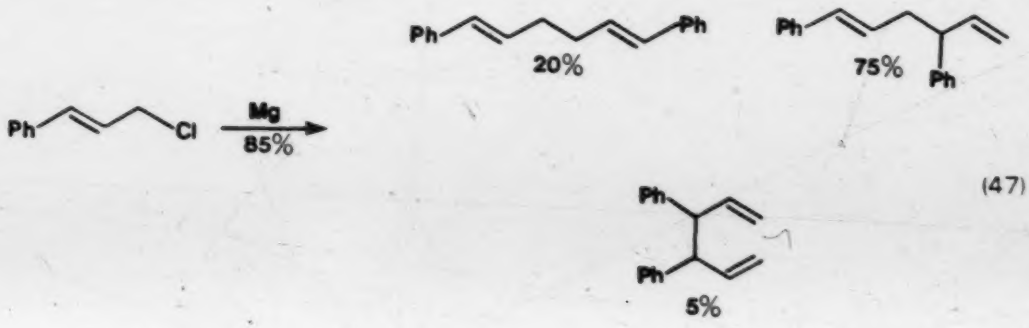
The coupling of allylic halides to form 1,5-dienes is synthetically important because of the frequent occurrence in nature of the 1,5-diene system, particularly in acyclic polyisoprenoids. A large number of reagents have been described which accomplish this transformation. For the most part, however, they suffer from three shortcomings. Allylic transposition of one or both of the allyl units is often observed during the coupling. Geometrical isomerization of the allylic double bonds is also frequently seen. Finally, most reagents show no specificity for the coupling of unlike allylic substrates.

The coupling of allylic halides over magnesium is a well known process (for some examples see references 56-63). In fact, it is often a competing reaction during the

preparation of allylic Grignard reagents.[56] The reaction usually gives mixtures of stereoisomers, mainly those resulting from head to tail joining of the allyl units (for example, equations 46 and 47).[57]



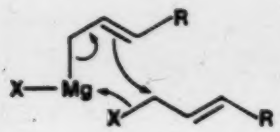
(46)



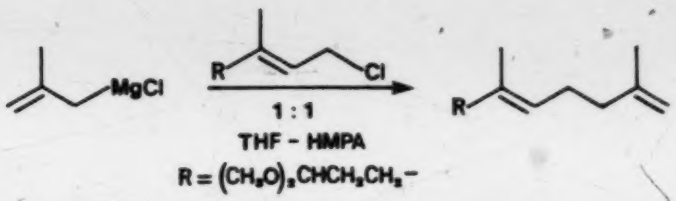
(47)

A cyclic transition state (Figure 2) has been proposed to account for the regiochemistry.[57, 58]

Figure 2



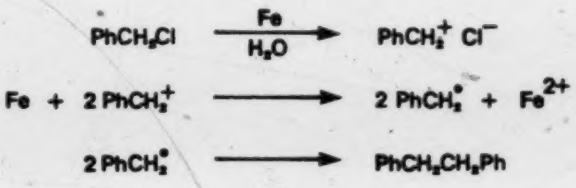
It is possible to perform cross coupling reactions of unlike allylic units with head to head coupling by treating an allylic halide in 1:1 THF-HMPA with the Grignard reagent of another allylic halide (equation 48).[64, 65] Without HMPA, considerable coupling at the tertiary center is observed. This result was explained by assuming that coordination of HMPA with the magnesium atom prevents allylic rearrangement.[64]



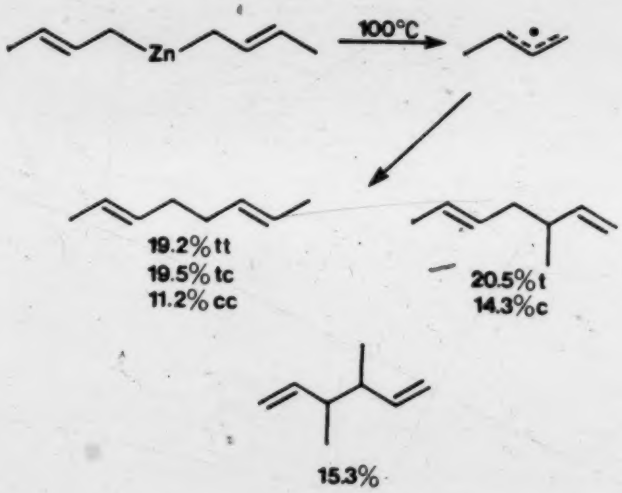
(48)

A number of other elemental metals have been used to couple allylic and benzylic halides. These include zinc,[66] aluminum,[67] sodium amalgam in DMF,[68] and chemically activated powders of nickel, cobalt, platinum, and iron prepared by reduction of the metal halide with potassium or lithium in the presence of naphthalene.[69] Iron powder has been used in water[70,71] and in DMF[72] to couple allylic and benzylic halides. In this case, the reaction is believed to proceed by the pathway shown in Scheme 10.[70]

Scheme 10

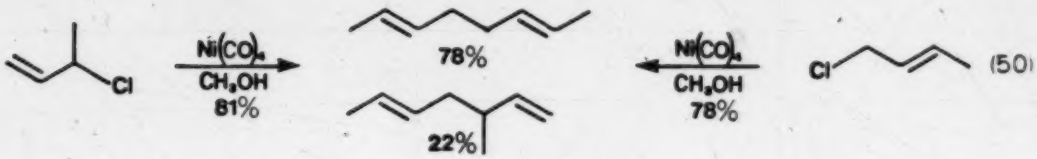


Bisallyl zinc compounds are thermally unstable and extrude zinc on heating.[73] The reaction was shown by CIDNP to proceed through allylic radicals and, as expected on the basis of such a mechanism, a mixture of isomeric products is obtained (equation 49).

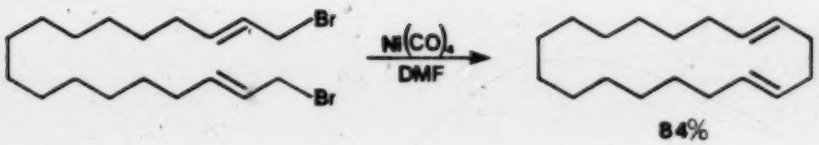


(49)

Another reagent that has been used extensively for coupling allylic halides (as well as tosylates and acetates) is tetracarbonylnickel.[74-77] Allylic alcohols and ethers are inert. With unsymmetrical substrates, the diene products are richer in the isomer which involves coupling at the less substituted end. Isomeric substrates give identical product mixtures (equation 50).[75] The reaction works well intramolecularly: 11-20 membered rings can be prepared in good yield (equation 51) under conditions of high dilution.[76]

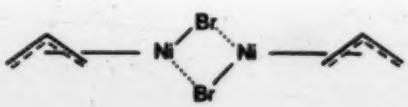


(50)



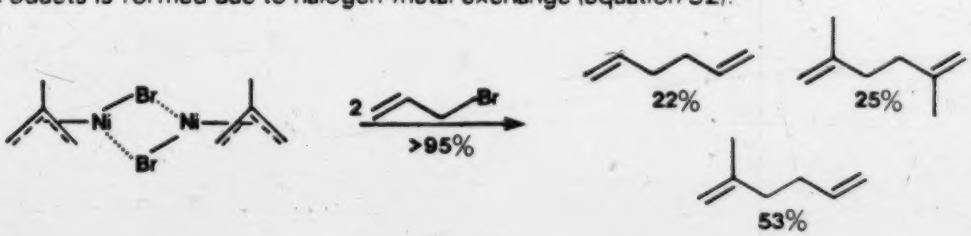
(51)

The reaction is thought to proceed via a dimeric π-allyl nickel complex (**10**).



10

Unsymmetrical coupling may be achieved by treating the complex with alkyl halides. However, when the complex is treated with an allylic halide, an almost statistical mixture of products is formed due to halogen-metal exchange (equation 52).[77]

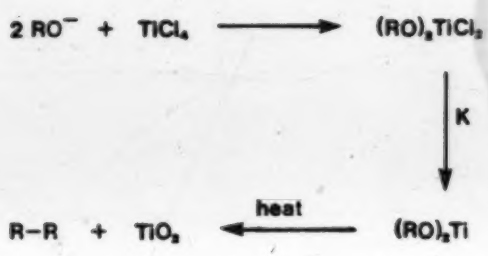


(52)

The major drawback to the use of this procedure is the volatility and toxicity of tetracarbonylnickel. This problem can be circumvented however, by employing biscyclooctadienylnickel as a source of Ni^0.[79] It appears to be more reactive and less hazardous than tetracarbonylnickel.

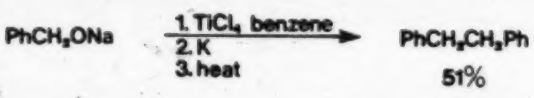
Allylic and benzylic alcohols have been symmetrically coupled using low valent titanium.[79-85] Initially, this reaction was carried out by treating an alkoxide with 0.5 equivalents of titanium tetrachloride. The resulting dichlorotitanium (IV) dialkoxide was then reduced with potassium metal to the titanium (II) dialkoxide. The latter thermally decomposes to the coupled hydrocarbon and titanium dioxide (Scheme 11).[79] The reaction was later modified to treatment of a monochlorotitanium(III) dialkoxide with methyllithium as reducing agent.[80]

Scheme 11

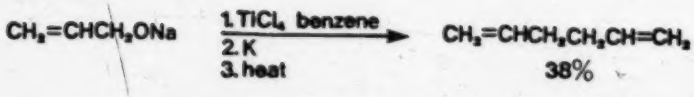


R = allyl, benzyl

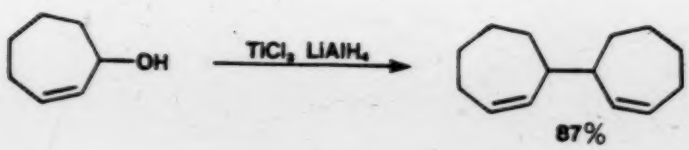
A much more convenient system which has been used extensively to generate Ti(III) species is $TiCl_3/LiAlH_4$.[81-84] Some examples of the use of low valent titanium to couple allylic and benzylic alchols are shown in equations 53-57.



(53)[79]

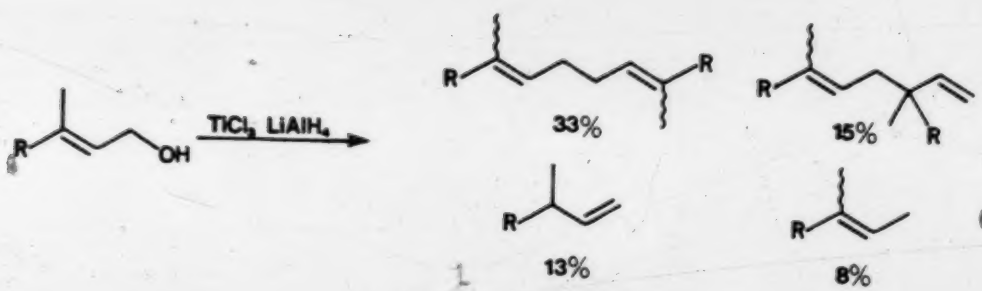


(54)[79]



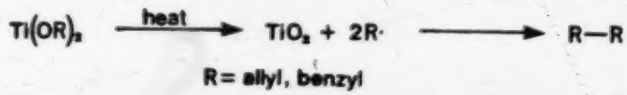
(55)[13]

(56)[13]



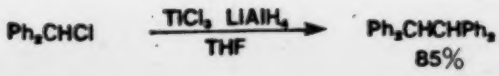
(57)[13]

The mechanism proposed for this sequence is a homolytic cleavage of the allylic carbon-oxygen bond of the titanium dialkoxide to produce two allylic radicals which then dimerize (equation 58).[15] As expected from a radical mechanism, allylic rearrangement is observed and a mixture of regio- and geometrical isomers is obtained. When the reaction is performed on a mixture of two different alcohols, an approximately statistical distribution of products is generated.

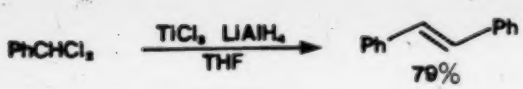


(58)

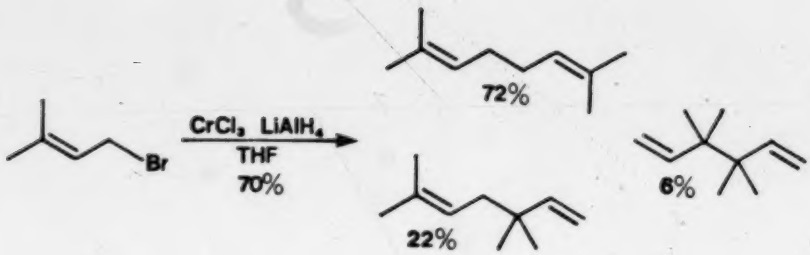
The reagents $TiCl_3/LiAlH_4$ or $TiCl_4/LiAlH_4$ have also been used to couple allylic and benzylic halides,[16] as have similar systems of $CrCl_3/LiAlH_4$[17] and $VCl_3/LiAlH_4$[13] (equations 59-64).



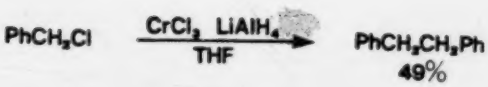
(59)[54]



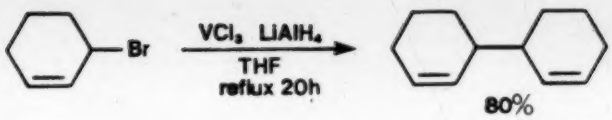
(60)[54]



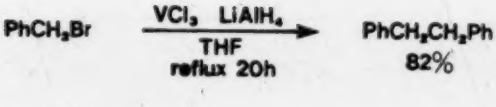
(61)[54]



(62)[54]



(63)[55]

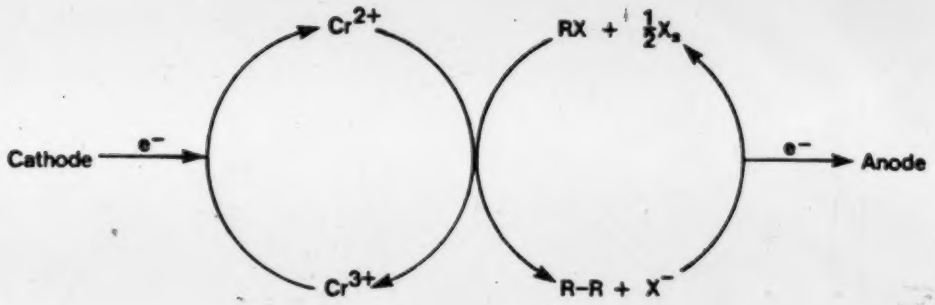


(64)[55]

These reactions probably proceed via electron transfer from the metal to the allylic halide.[56]

Chromous salts have been used catalytically in an electrochemical process (Scheme 12).[57]

Scheme 12



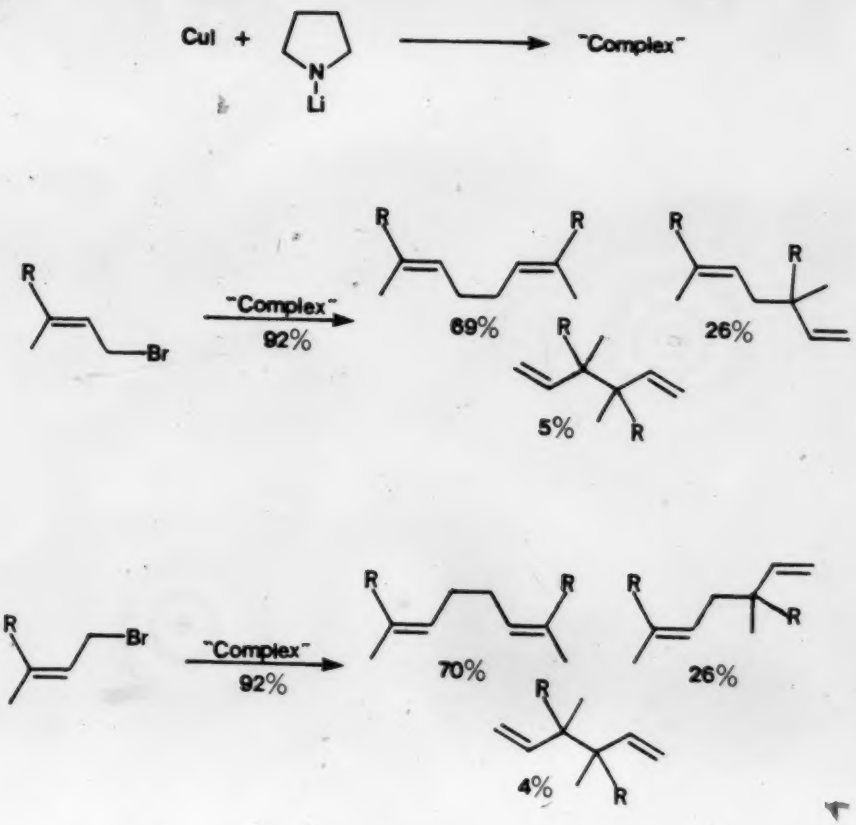
R=Allyl, Benzyl **X=Cl, Br**

Yields are as good as, or better than, those obtained with the $CrCl_3/LiAlH_4$ reagent and the process requires only a catalytic amount of the chromium species.

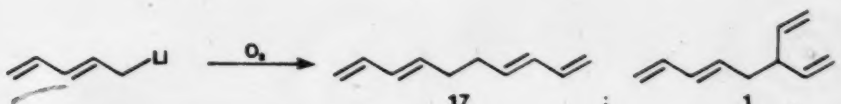
The transition metal complexes $Cr(ClO_4)_2$,[90] $V(Cp)_2$,[91] Py_4VCl_2,[92] $(PPh_3)_3CoCl$,[93] $Fe(CO)_{12}$-pyNO complex,[94] and SmI_2[95] are also known to couple allylic and/or benzylic halides. Cuprous chloride in DMSO performs a similar function.[96]

A complex generated by reaction of cuprous iodide with lithium dialkyl amides couples allylic halides and affords mixtures of regioisomers. However, unlike other procedures, this one is completely stereospecific (Scheme 13).[97]

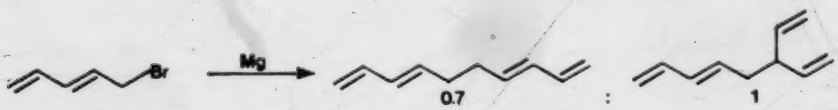
Scheme 13



Allylic organometallics can be coupled by oxidation using air or oxygen.[91 99] The presence of $CoCl_2$ often favours formation of dienes.[100] The latter may be formed by dimerization of allylic radicals produced at some stage of the oxidation. The product distribution is markedly different from that observed when the coupling is performed over magnesium (equations 65 and 66).

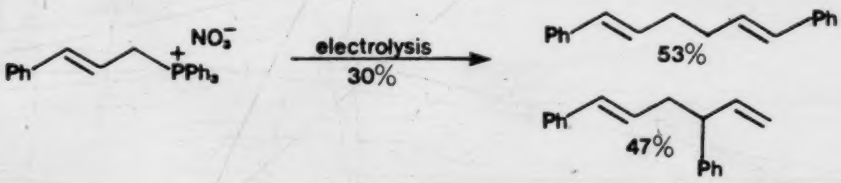


(65)[99]

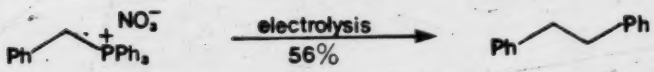


(66)[41]

Allylic and benzylic phosphonium salts can be coupled in low yield by electrochemical means (equations 67 and 68).[101]



(67)

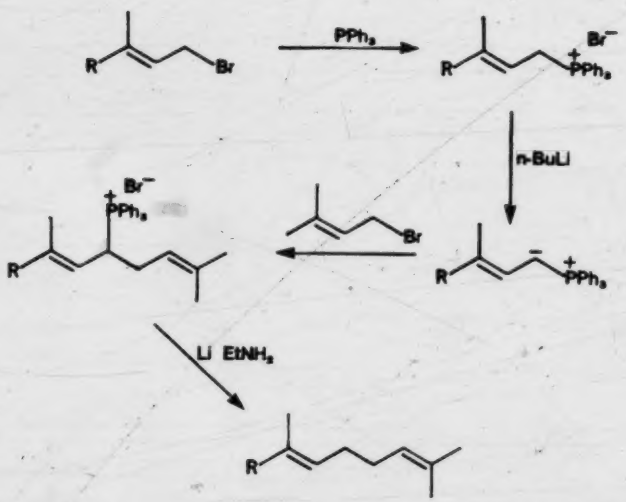


(68)

The lack of regiochemical and stereochemical control exhibited by most of the above reactions, and the desire to couple different allylic units encouraged attempts to develop additional procedures.

In one such reaction, a phosphonium ylide (derived from one allylic halide) is coupled with another allylic halide. The product is a phosphonium salt which must be reduced to the hydrocarbon (Scheme 14).[102]

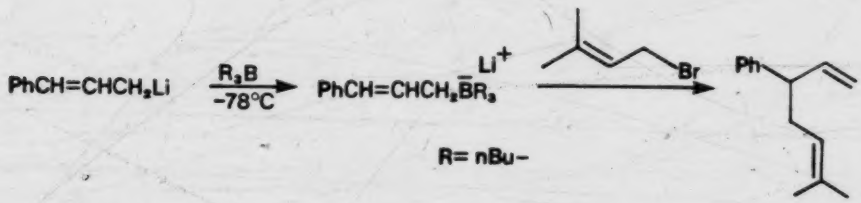
Scheme 14



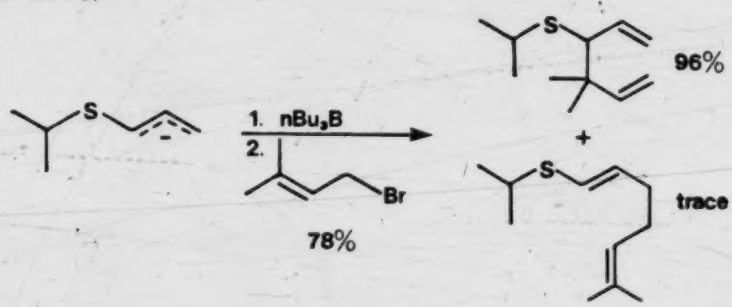
This reaction preserves the position and geometry of the double bonds of both units.

Towards the same end, an allylic halide can be used to alkylate the anion derived from an allyl phenyl thioether[103-107] or an allyl aryl sulfone.[108 109] Here, a phenylthio or arylsulfone group must be removed to give the 1,5-diene. In favourable cases, the position and geometry of the double bonds are preserved.

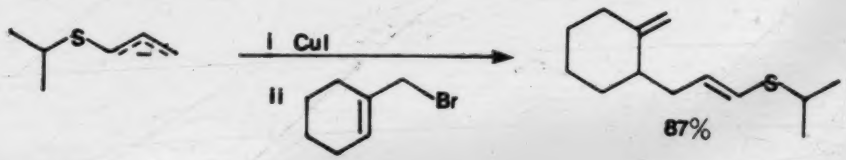
Regiocontrolled head to tail coupling has been accomplished with allylic boron "ate" complexes (equation 69).[110]



Similar regiocontrol is observed when trialkylboranes are added to lithiated allyl sulfides equation 70).[111]

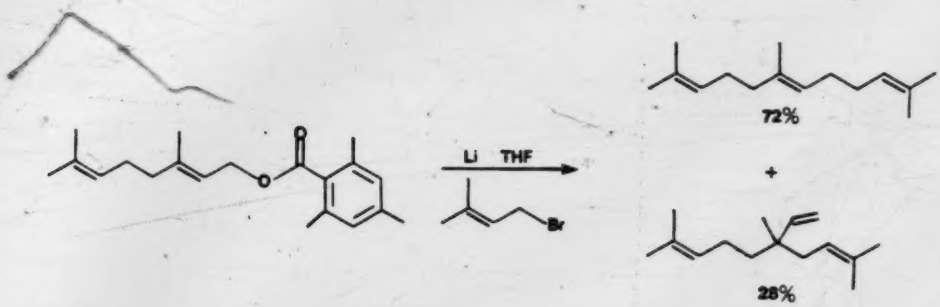


Completely different behavior is seen when cuprous iodide is added to the alkylthioallyl anion (equation 71).[112] The alkylation is γ to the sulfur and involves SN_2' attack on the allylic halide.



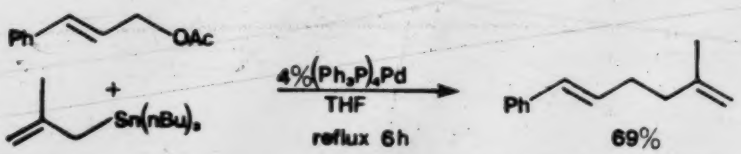
(71)

Cross coupling has been accomplished by *in situ* generation of a lithiated allyl anion from an allyl mesitoate in the presence of an allylic halide. The products show allylic transposition of the anion portion only (equation 72).[113 114]

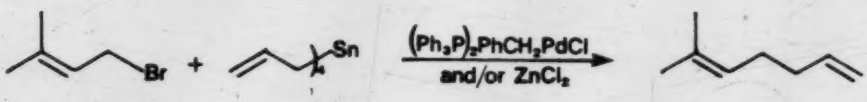


(72)

Allylic halides and acetates react with allylstananes in the presence of palladium and zinc catalysts (equations 73 and74).[115 116]



(73)[115]

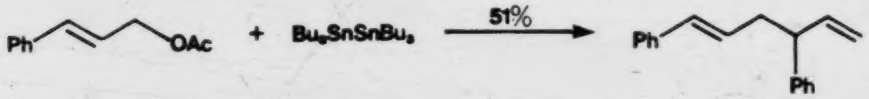


(74)[116]

The reaction is thought to involve π-allyl metal complexes and proceeds with inversion of the stanane (Figure 3).

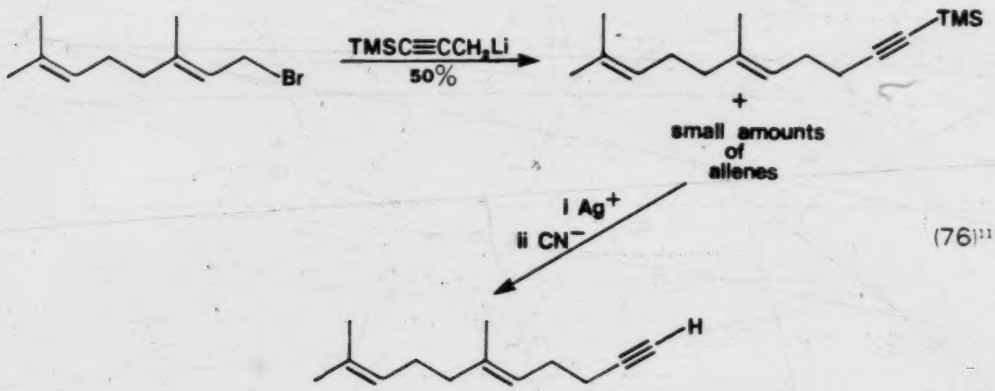
Figure 3

Symmetrical couplings can also be performed (equation 75).[115]



(75)

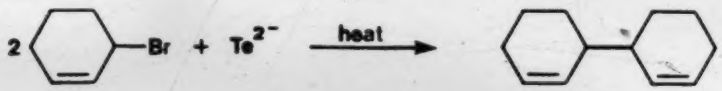
The coupling of propargylic compounds with allylic substrates gives 1,5-enynes which can be partially reduced to1,5-dienes. A number of procedures have been developed which generate 1,5-enynes in a regio- and stereochemically specific manner (for example equation 76).[117-126]



(76)[117]

II. RESULTS AND DISCUSSION*

We examined the response of allylic halides to Te^{2-} and found that the reaction can be used to prepare 1, 5-dienes according to equation 77.



(77)

A variety of allylic chlorides and bromides were examined and they generaly afforded good to excellent yields of coupled products (Table 1).

While the reaction does require scrupulous attention to the exclusion of air, the procedure is simple to perform. The extremely air sensitive Te^{2-} reagent,** is most conveniently generated *in situ*, by a procedure analogous to that used for the preparation of the corresponding S^{2-} [121] and Se^{2-} [122] reagents. One simply injects a commercial solution of Super-Hydride*** onto a stirred portion of powdered tellurium under an atmosphere of argon. The metal dissolves over a period of a few hours to give a white suspension of lithium telluride (equation 78).

$$Te + 2LiEt_3BH \longrightarrow Li_2Te + 2BEt_3 + H_2 \qquad (78)$$

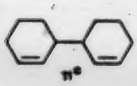
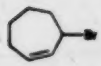
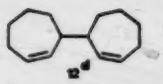
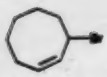
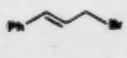
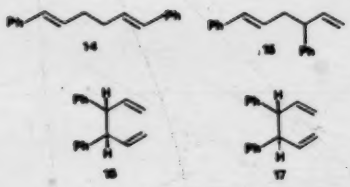
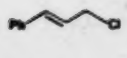
A dioxane solution of two moles of the allylic halide per mole of lithium telluride is then added and the mixture is heated at reflux for the time specified in Table 1 - usually 1 h. During this period, tellurium metal is deposited. The coupled products are then isolated by chromatography and distillation. The progress of the reaction can be very approximately monitored by thin layer chromatography (TLC). If the reaction is incomplete, a black streak appears on the TLC plate; presumably, this is a result of decomposition of a tellurium species during development of the chromatogram. We established that the optimum relative molar proportions of Super-Hydride / tellurium / allylic halide is 2.6:1:2.

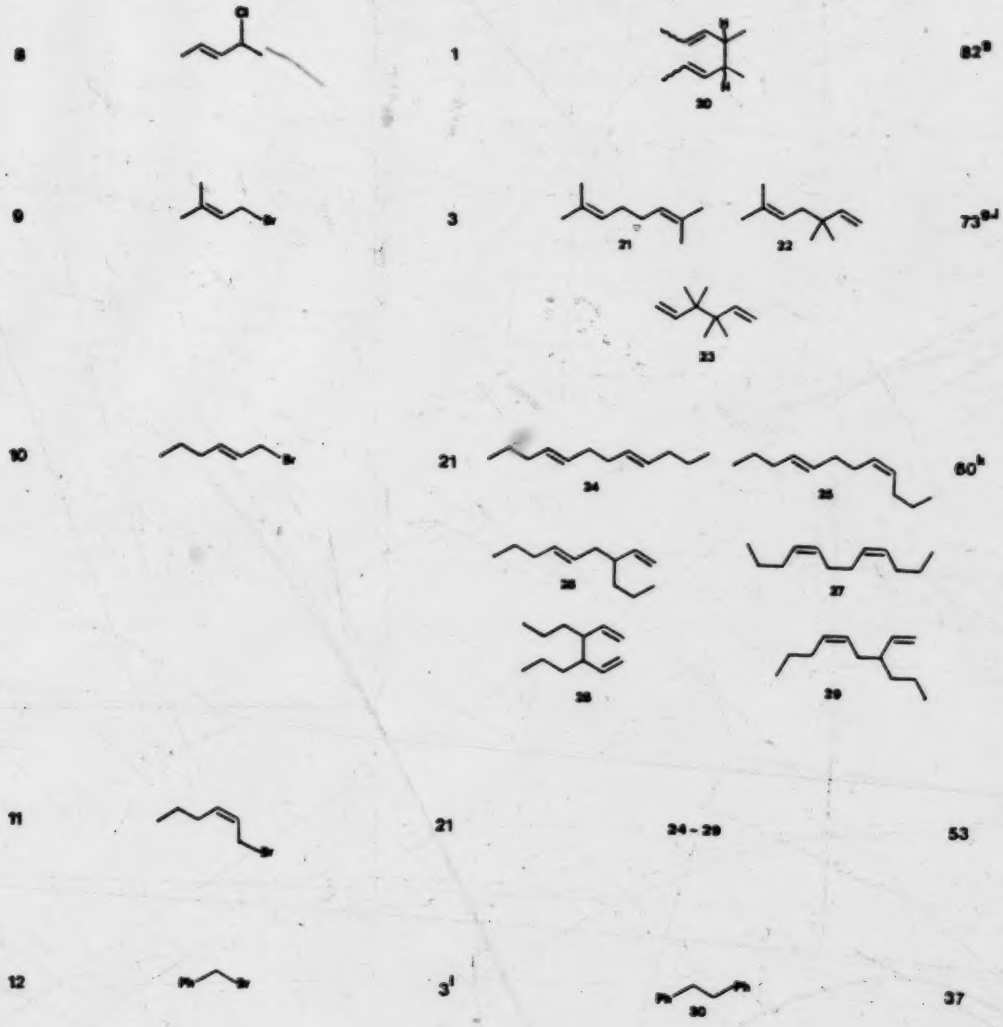
---

*Some of these results have been published.[55]
**This reagent may be prepared by a number of other procedures,[2,123] or purchased commercially.
***Aldrich trademark for a 1 M solution of lithium triethylborohydride in THF.[124]

Table 1

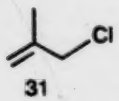
Coupling of Allylic Halides Using Te[a]

entry	allylic halide	reflux time h[b]	products	% yield[b]
1		1	 11[c]	86
2		1	11	81
3		1	 12[d]	86
4		1	13[c]	81
5		1	 14 15 16 17	91[e]
6		1	14 - 17	93[e]
7		1[f]	18 19	82[g,h]

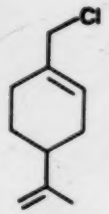


Footnotes to Table 1: a) Unless indicated otherwise, reactions were performed in a mixture of THF and dioxane (*ca.* 2:3 by volume), and the solution was heated in an oil bath at 110°C.
b) Yields refer to isolated products except where indicated otherwise.
c) *Meso*/*dl* ratio of 1:1 (^{13}C NMR; isolation).
d) *Meso* and *dl*.
e) (**16** + **17**)/**15**/**14** ratio of 1:3.9:3.0 (NMR).
f) Reaction run in THF only, with an oil bath set at 80°C.
g) VPC yield.
h) **18**/**19** ratio of 1.3:1 (VPC).
i) **21**/(**22** + **23**) ratio of 1.4:1 (VPC).
j) *Meso* and *dl* isomers.
k) **28**/**27**/**29**/**24**/**25**/**26** ratio of 1:1.2:1.7:3.5:3.5:3.6 (determined by a combination of VPC and isolation).
l) Mixture heated in a sealed tube at 160°C.

In addition to the examples shown in Table 1, we also attempted to couple 3-chloro-2-methyl-1-propene (**31**), 1-(chloromethyl)-4-(1-methylethenyl)-cyclohexene (**32**), and 1-bromo-2-hexyne (**33**). While these halides all appeared to react completely with the tellurium reagent (TLC), extrusion of tellurium from the resultant species was very slow and attempts to isolate hydrocarbon products were unpromising. In the case of (bromomethyl)benzene, which behaved similarly under the standard reaction conditions, the effect of using a higher reaction temperature was also examined. The reaction mixture was heated for 3 h in a sealed tube at 160°C and some coupled product **30** (37%) was obtained.



31



32

33

As can be seen from the results in Table 1, the reaction is neither regio- nor stereospecific. It proceeds with scrambling of both the original position and geometry of the double bonds (entries 5-11). Chlorides and bromides give similar yields and similar isomer distributions (entries 1 and 2; 5 and 6). In the case of the geometrically isomeric 1-bromo-2-hexenes (entries 10 and 11), similar yields and identical isomer ratios were obtained.

All of the products were identified spectroscopically although individual assignments of *meso* and *dl* stereochemistries were not made in most cases. For the *meso* and *dl* isomers of 2,2'-bicyclohexenyl (**11**), it was possible to assign tentatively relative stereochemistry using an argument that had been published for a similar problem with *meso*- and *dl*-2,2'-bicyclopentenyl (**34**).[125] The diastereoisomers of the latter showed identical NMR spectra except for fine splitting in the olefinic region (Figure 4).

34

Figure 4

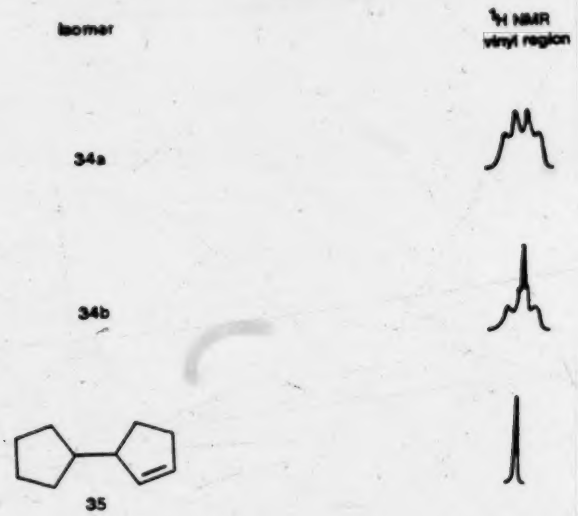


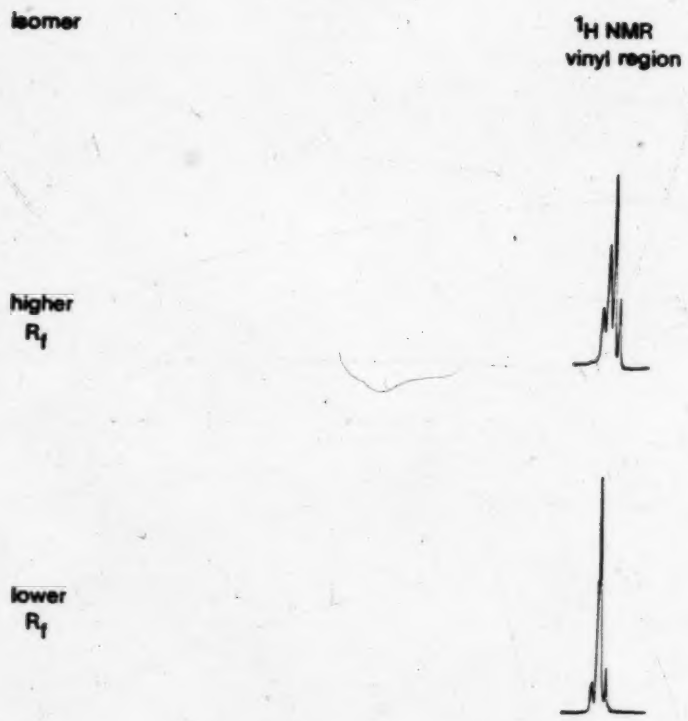
Figure 5

meso-34 dl-34

Significantly, the olefinic splitting of one isomer (**34b**) resembled that of the partial hydrogenation product **35**. The expected most favourable conformations of the *meso* and *dl* isomers of **34** are shown in Figure 5. The olefinic hydrogens of the *meso* isomer in which the double bonds are on opposite sides of the molecule, have an environment most closely resembling that of the olefinic hydrogens of the partially hydrogenated product **35**. On this basis, compound **34b** was judged to have *meso* stereochemistry. The isomer **34a** exhibiting the larger olefinic splitting was therefore formulated as the *dl* isomer.

Examination of the vinyl region of the NMR spectra of the separated diastereoisomers of 2,2'-bicyclohexenyl (**11**), shows similar differences in olefinic splitting (Figure 6). On this basis, we have assigned for the isomer of higher Rf, the *dl* configuration, and for the compound having lower Rf, the *meso* configuration. It was not possible to separate the diastereoisomers of 2,2'-bicycloheptenyl (**12**) and the separated diastereoisomers of 2,2'-bicyclooctenyl (**13**) did not show comparable differences in the

Figure 6



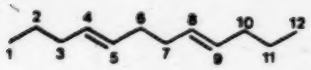
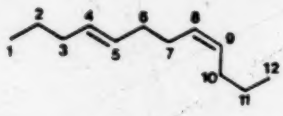
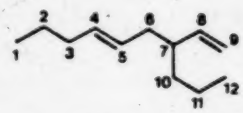
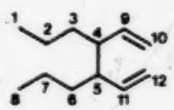
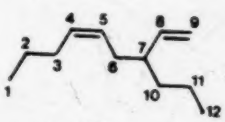
olefinic region of their spectra.

In the case of *meso*- and *dl*-3, 4-diphenyl-1, 5-hexadiene (**16** and **17**) it was possible to assign relative stereochemistry to the separated diastereisomers by comparison of their melting points with those reported for authentic samples prepared independently in a stereochemically unambiguous fashion.[126]

For the identification of compounds **24** to **29** which could not be completely separated (see Experimental), ^{13}C NMR spectroscopy proved to be particularly useful. It was possible to assign the structures of these compounds from the close correspondence of their ^{13}C NMR spectra with those calculated by empirical means (Table 2).

Table 2

^{13}C NMR Chemical Shifts (δ) for Compounds 24-29

Carbon	Observed and (Calculated)*					
						
	24		**25**		**26**	
1	13.6	(13.9)	13.7	(13.9)	14.1	(13.9)
2	22.7	(22.7)	22.7[a]	(22.7)	22.8	(22.7)
3	34.8	(32.4)	34.8	(32.4)	34.8	(32.4)
4	130.0[a]	(131.4)	130.6[b]	(131.4)	131.6	(132.9)
5	130.5[a]	(131.4)	130.0[b]	(131.4)	128.4	(129.9)
6	32.8	(30.0)	32.8	(30.0)	36.4	(34.2)
7	32.8	(30.0)	27.5	(24.0)	43.9	(39.1)
8	130.5[b]	(131.4)	130.0[b]	(130.3)	143.1	(145.3)
9	130.0[b]	(131.4)	129.4[b]	(130.3)	113.8	(114.8)
10	34.8	(32.4)	29.4	(26.4)	38.3	(36.6)
11	22.7	(22.7)	22.9[a]	(22.7)	20.2	(20.2)
12	13.6	(13.9)	13.7	(13.9)	14.1	(14.4)
						
	27		**28**		**29**	
1	13.6	(13.9)	13.8	(14.4)	14.2	(13.9)
2	22.9	(22.7)	20.5	(20.2)	22.9	(22.7)
3	29.4	(26.4)	34.0	(34.2)	29.5	(26.4)
4	129.4[a]	(130.3)	48.6	(41.6)	130.5	(131.8)
5	130.1[a]	(130.3)	48.6	(41.6)	128.0	(128.8)
6	27.5	(24.0)	34.0	(34.2)	32.7	(28.2)
7	27.5	(24.0)	20.5	(20.2)	44.0	(39.1)
8	130.1[b]	(130.3)	13.8	(14.4)	143.1	(145.3)
9	129.4[b]	(130.3)	141.8	(143.8)	113.9	(114.8)
10	29.4	(26.4)	115.0	(116.3)	36.6	(36.6)
11	22.9	(22.7)	141.8	(143.8)	20.3	(20.2)
12	13.6	(13.9)	115.0	(116.3	14.2	(14.4)

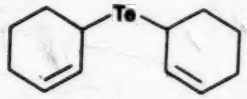
a, b – These assignments may be interchanged.

* – See Appendix for calculations.

Mechanistic Considerations. Using 3-bromocyclohexene as a test case, we examined the role of triethylborane in the reaction mixture. Using commercial lithium telluride, the coupling of 3-bromocyclohexene was performed both in the presence, and absence, of two equivalents of triethylborane. The reactions gave similar yields (39% and 29% respectively) of 2,2'-bicyclohexenyl (**11**). The yields were lower than that for the reaction performed using Te^{2-} prepared *in situ*. This difference probably reflects the inferior quality of the commercial reagent which must undergo several transfer operations (with protection from air) before reacting with the halide. The commercial material is also likely to be in a different state of subdivision than reagent generated *in situ*. These experiments serve to demonstrate that triethylborane in the reaction mixture has no substantive effect on the coupling.

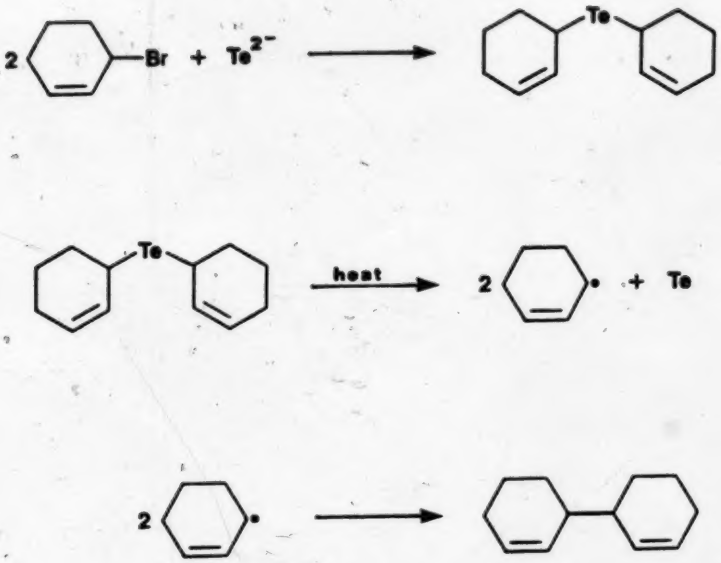
A number of observations suggest a three step mechanism for this coupling reaction (Scheme 15). The first stage involves nucleophilic displacement of bromide by telluride to give a bisallylic telluride. This then thermally extrudes tellurium to produce two allylic radicals, which recombine to give the observed products.

A conceivable alternative mechanism for this reaction would involve an electron transfer from Te^{2-} to the allylic halide to give a radical anion, which would lose halide and thereby generate an allylic radical (Scheme 16). This pathway would not involve an intermediate bisallylic telluride and was excluded on the basis of the following experiments which served to detect an intermediate. A solution of 3-bromocyclohexene in THF was added to a suspension of the Te^{2-} reagent at room temperature, to afford a clear solution. ^{13}C NMR analysis of this solution showed, in place of the diagnostically characteristic signals (see Experimental) for 3-bromocyclohexene and 2,2'-bicyclohexenyl (**11**), new signals at δ 125.8, 125.9, 130.6 and 130.7. We attribute these to the sensitive bisallylic telluride **36** (*meso* and *dl* forms).

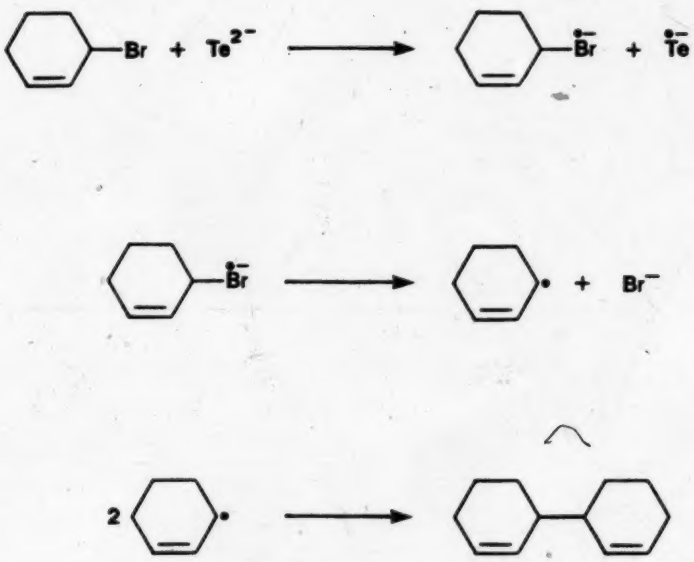


36

Scheme 15



Scheme 16



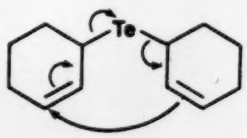
In a separate experiment, the same solution of allylic halide and Te^{2-} in THF was kept at room temperature for 1 h (about twice the time period which had elapsed before

measuring the ^{13}C NMR spectrum), diluted with dioxane* and refluxed for 1 h. The isolated yield of 2,2'-bicyclohexenyl (**11**) was 82%. Clearly, an initial reaction period at room temperature* has no substantive effect on the course of the coupling reaction.

On the basis of this evidence, we conclude that bisallylic tellurides formed by ionic displacement of halide by telluride are intermediates, and that the reaction does not proceed, at least as a major pathway, by electron transfer between Te^{2-} and the allylic halide. The formation of a bisallylic telluride is also consistent with the observation that similar product yields and isomer ratios are obtained from allylic halides irrespective of the nature of the halogen (entries 1 and 2, 5 and 6).

Thermal extrusion of tellurium from the proposed intermediate could, in principle, occur by two distinct pathways. The telluride could decompose by homolytic fragmentation to radicals, as described above, or alternatively the telluride could decompose in a concerted, cheletropic fashion (Figure 7).

Figure 7



We feel that our observations favour the radical pathway. Direct spectroscopic detection of radical intermediates would of course be the best evidence; however, attempts to observe such species by ESR failed. The solution in which the bisallylic telluride **36** was formed showed no ESR signal either at room temperature or at 100°C. At the higher temperature, tellurium was deposited.

Indirect evidence consistent with the radical pathway was obtained from the following cross coupling experiment. Two THF solutions, one of 3-bromocyclohexene and the Te^{2-} reagent and one of 3-bromocycloheptene and the Te^{2-} reagent, were prepared in the usual fashion and stirred at room temperature. Aliquots of each clear solution were mixed, diluted with dioxane** and refluxed for 1 h. Isolation of the 2,2'-bicycloalkenyls (67% after distillation, calculation based upon the size of aliquots taken) gave material consisting of three resolvable (VPC) components, in a ratio of

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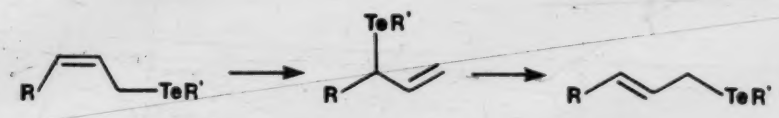
*In our preparative runs, we refluxed the mixture *soon after* mixing the reagents.
**The proportion of dioxane was the same as in the preparative runs.

1:1.3:1.* VPC/MS served to identify the components as 2,2'-bicyclohexenyl (**11**), 3-(2-cyclohexenyl)cycloheptene and 2,2'-bicycloheptenyl (**12**) respectively. These results are clearly consistent with the presence of cyclohexenyl and cycloheptenyl radicals. The non-statistical ratio of products (expected ratio 1:2:1) can be explained as a mixing phenomenon. Two radicals of the same type are formed in the same region of space (from one molecule of bisallylic telluride) and thus have a greater than statistical chance of recombining than do two radicals of different type (from different bisallylic tellurides). This experiment is clearly consistent with a radical mechanism, however, it does not exclude the possibility of ligand exchange between two different symmetrical bisallylic tellurides before the thermal extrusion of tellurium. This type of behavior has been observed during the thermal decomposition of tetraaryl tellurides,[37,38] but is unprecedented for dialkyl tellurides.

Further indirect evidence was also found in favour of a radical mechanism. Allylic radicals would be expected to give products resulting from allylic rearrangements. This is amply demonstrated by entries 5-11. Moreover, allylic radicals are known to undergo geometrical isomerization fairly readily,[127-130] and we observed that the geometrically isomeric 1-bromo-2-hexenes (entries 10 and 11) gave identical product mixtures. However, it must be noted that isomerization of the double bond could occur, in principle, also by a 1,3-tellura-shift (equation 79).



(79)

The stability of an allylic radical, and hence its ease of formation, should be enhanced by substituents, particularly those in the 1- and 3- positions (Figure 8). Our qualitative observations are that reactions involving allylic halides which would lead to secondary-secondary (entries 1-4 and 8) and primary-tertiary (entry 9) radicals proceed more readily (shorter reaction times and higher yields) than those which would involve primary-secondary (entries 10, 11 and 1-(chloromethyl)-4-(1-methylethenyl)-1-cyclohexene (**32**)), primary-primary (3-chloro-2-methyl-1-propene (**31**)), benzyl (entry 12), or

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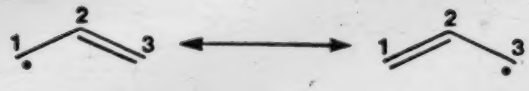
*Relative peak areas.

Figure 8

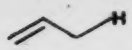
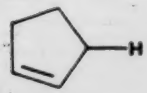
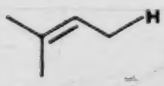


propargyl (1-bromo-2-hexyne (**33**)) radicals. Also, cases where especially stabilized radicals would be formed (entries 5-7) undergo the reaction very easily.

The allylic, benzylic or propargylic carbon-hydrogen bond dissociation energies of some unsaturated hydrocarbons are shown in Table 3. If the same trend exists for carbon-tellurium bond dissociation energies, then it is qualitatively similar to our observed order in ease of reactivity of various substrates.

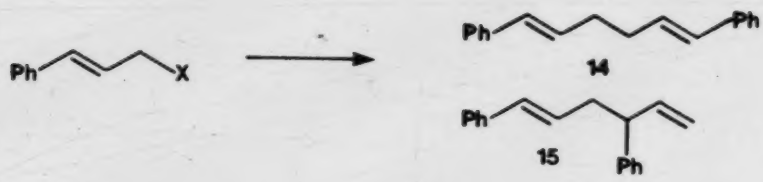
Table 3

Carbon-Hydrogen Bond Dissociation Energies for Some Unsaturated Hydrocarbons

Compound	BDE (kcal mol^{-1})	Ref.
	93.9 ± 1.2	131
	89± 1	132
	85 ± 1	132
	83 ± 1	132
	82.3 ± 1	133
	77.2 ± 1.5	134

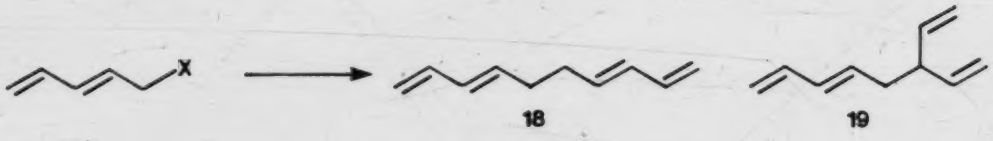
Further indirect evidence for radical intermediates comes from the similarity seen in the product isomer ratios from our tellurium coupling procedure and from other reactions thought to proceed through radical intermediates. Conversely, the product ratios seen in the tellurium coupling reaction are quite different from those obtained from

magnesium couplings, thought to proceed via a cyclic, concerted mechanism (equations 80, 81 and 82).



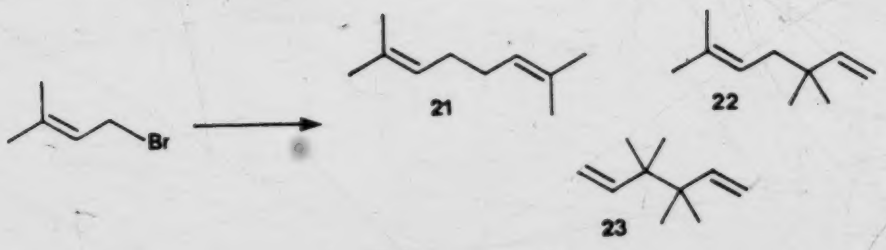
(80)

coupling method	product ratio 14:15:16, 17	ref.
Te^{2-} (X = Br, Cl)	49:38:13	55
electrochemical (X = $^{\cdot}PPh_3NO_2^-$)	52:48:-	101
Mg (X = Cl)	20:75:3-5	57



(81)

coupling method	product ratio 18:19	ref.
Te^{2-} (X = Cl)	1.3:1	55
O_2(X = Li)	1.7:1	99
Mg (X = Br)	0.7:1	63

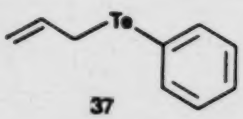


(82)

coupling method	product ratio **21:22:23**	ref.
Te^{2-}	58:42 (**21:22+23**)	55
$CrCl_3/LiAlH_4$	72:22:6	87
Mg	-:major:-	58

Since allylic sulfides[125] and selenides[126] are known to undergo 1,3-allylic shifts, we briefly examined this aspect of allylic telluride chemistry. When (3-bromo-1-propenyl) benzene was treated with a suspension of Li_2Te_2, prepared from the appropriate proportions of Super-Hydride and tellurium (see Experimental), an immediate precipitation of tellurium occurred. After the usual reflux period (1 h), during which more tellurium was deposited, the coupled products **14-17** were isolated (88% yield) and found to be in the same proportions as the couplings with Te^{2-}. This experiment is consistent with radical path *a* (Scheme 17) and also with path *b* involving 1,3-allylic shifts. For convenience, the incursion of 1, 3-allylic shifts is shown only at stage *b* but can in principle occur at an earlier stage. Similarly, SN_2' reactions, while conceivable, are not shown.

A few additional comments of a mechanistic nature are in order. For the coupling reaction to occur under the comparatively mild conditions of this procedure, both carbon-tellurium bonds should be allylic. This requirement is demonstrated by the observations that (2-propenyltelluro)benzene (**37**) is a distillable liquid (bp 62°C, 0.3 mm),[43] and the telluride **8** in which both allylic carbon-tellurium bonds are not coplanar with the π bonds requires a high temperature (175°C) for extrusion of tellurium (equation 45).

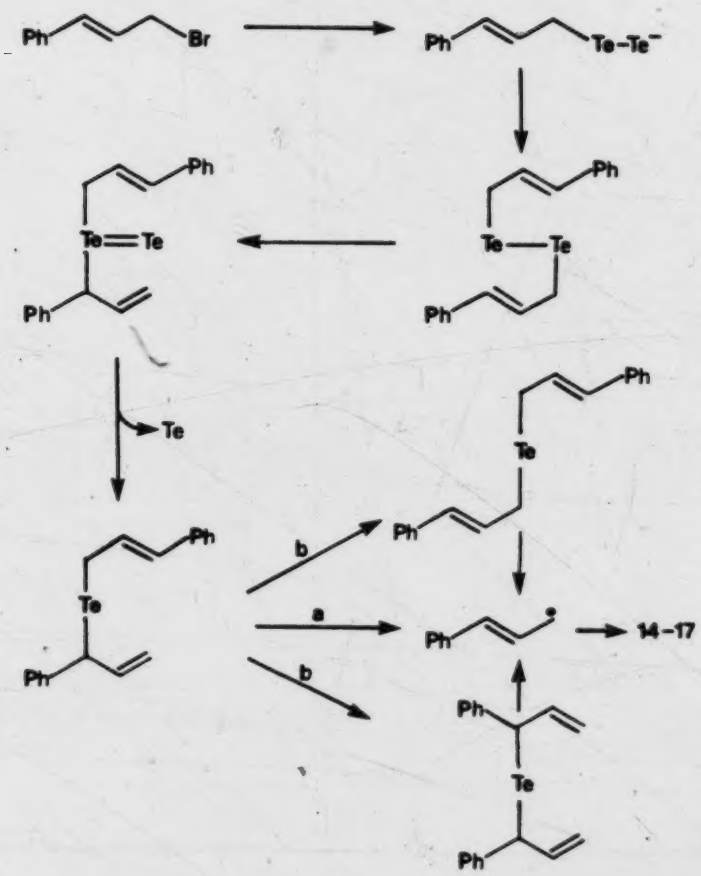


37

8

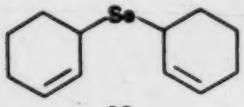
Our reaction does proceed in refluxing THF, but gives more reproducible results if a THF-dioxane mixture is used. This is presumably a consequence of the higher reflux temperature.

Scheme 17



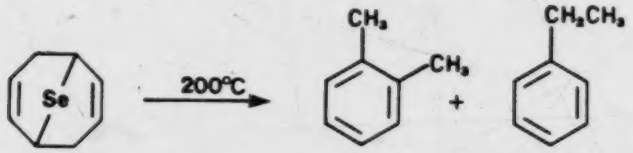
Finally, this reaction demonstrates a property of tellurium not shared, at least in adequate degree, by selenium. A comparable experiment using 3-bromocyclohexene and Se^{2-} gave only selenide **38**, as a mixture of diastereoisomers with less than 2% (VPC) of the

coupled product 2,2'-bicyclohexenyl (**11**).



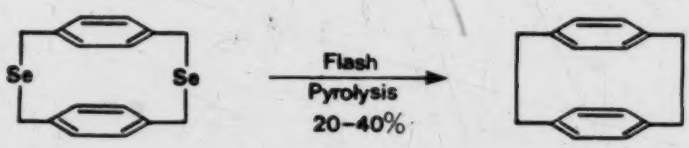
38

Furthermore, the selenium analogue of compound **8** decomposes slowly at 200°C to *o*-xylene and ethylbenzene (equation 83).[137]



(83)

An example of the thermal extrusion of selenium to give bibenzyl products is shown in equation 84.[138] This, however does not seem to be a generally useful process for the coupling of allylic and benzylic halides.



(84)

The greater ease of extrusion of tellurium from bisallylic or bisbenzylic tellurides when compared with selenium, is not surprising in light of the known trend of decreasing bond strength as one descends a particular group in the periodic table (Table 4).

Table 4

Bond Strengths for Carbon Bonded to Some Group VI Elements

Bond	Kcal mol^{-1}	Ref.
C-O	85-91	139
C-S	69	140
C-Se	59	140
C-Te	(54)*	-

* Calculated using Pauling equation.[141]

Conclusions. The procedure decribed herein represents a new method for coupling allylic halides. The reaction appears to proceed via bisallylic tellurides which decompose thermally into allylic radicals. These then dimerize. The reaction generally gives good to excellent yields of coupled products and represents a new aspect of the use of tellurium in organic synthesis.

III. EXPERIMENTAL

General. Except where stated to the contrary, the following particulars apply: All experiments were performed under a slight static pressure of argon. All apparatus was oven dried overnight (120°C) and cooled in a desiccator over Drierite. Solvents for chromatography were distilled before use. Solvents for reactions were dried by distillation from a suitable drying agent under nitrogen, and were transferred by oven dried syringes. The stirring of reaction mixtures was accomplished by the use of Teflon coated magnetic stirring bars. During product isolation, solutions were dried (where necessary) with anhydrous magnesium sulfate and evaporated under water aspirator vacuum at room temperature. In those cases where compounds were isolated simply by evaporation of their solutions (and not also by subsequent distillation) the residues were kept under oil pump vacuum and checked for constancy of weight. Isolated products were submitted directly for combustion analysis, without need for further purification. Melting points (mp) were determined on a Kofler block melting point apparatus and are uncorrected. Boiling points (bp) reported for products distilled in a Kugelrohr apparatus refer to the oven temperature. Commercial thin layer chromatography (TLC) plates (silica gel Merck 60F-254) were used. Plates impregnated with silver nitrate were prepared from Merck silica gel 60PF-254. For such plates, the % silver nitrate refers to (weight of $AgNO_3$)/(weight of silica gel). For TLC, UV active spots were detected at 254 nm. Other spots were detected using iodine or by spraying the plate with 6 *N* sulfuric acid in methanol followed by charring on a hot plate. Silica gel for column chromatography was Merck type 60 (70-230 mesh). All vapour phase chromatographic (VPC) analyses were performed on a Hewlett-Packard 5830A gas chromatograph equipped with an FID detector using pre-packed Hewlett-Packard 6ft x 1/8 in o.d. stainless steel analytical columns, with nitrogen as the carrier gas. The column used for these analyses was 10% w/w Apiezon L; 2% KOH on acid washed Chromosorb W (80-100 mesh) at temperatures between 90 and 200°C. For yields evaluated by VPC, an internal standard was used and response factors compared to the standard were calculated for each component in the mixture to be analysed. Infrared (IR) spectra were recorded with a Perkin-Elmer model

297 spectrophotometer. Liquids and oils in general were run as neat films on sodium chloride plates. Solids were run as solutions in the given solvent using 0.5 mm sodium chloride solution cells. Only diagnostically significant peaks are reported. Proton nuclear magnetic resonance (NMR) spectra were recorded with Bruker WP-80 (at 80 MHz), Varian HA-100 (at 100 MHz), Bruker WP-200 (at 200 MHz) or Bruker WP-400 (at 400 MHz) spectrometers in the specified deuterated solvent with tetramethylsilane as an internal standard. Carbon-13 nuclear magnetic resonance (^{13}C NMR) spectra were recorded with Bruker WP-60 (at 15.08 MHz), Bruker HFX-90 (at 22.6 MHz), Bruker WH-200 (at 50.32 MHz) and Bruker WH-400 (at 100.64 MHz) spectrometers using deuteriochloroform as an internal standard. The following abbreviations are used with respect to NMR spectra: s = singlet, d = doublet, t = triplet, q = quartet, p = quintet, m = multiplet, br = broad. Mass spectra (MS) were recorded with an A.E.I. model MS 9, MS 12, or MS 50 mass spectrometer. Microanalyses were performed by the microanalytical laboratory of this department.

Materials. Dry dioxane, ether and tetrahydrofuran (THF) were distilled immediately before use from sodium and benzophenone ketyl. Dry *tert*-butyl alcohol was distilled immediately before use from calcium hydride. Commercial (Aldrich) *n*-butyllithium in hexane and methyllithium in ether were titrated before use by the diphenylacetic acid method.[142] Super-Hydride[124] was purchased as a 1 M solution in THF and used at the stated concentration. Hexamethylphosphoric triamide (HMPA) was distilled from calcium hydride under reduced pressure (0.1 mm). 4-Methylbenzenesulfonyl chloride was purified before use by a literature procedure.[143] Lithium chloride was dried by heating at 100°C under oil pump vacuum overnight. Commercial (Alfa) lithium telluride was stored under argon in the dark and was transferred to reaction vessels in a glove bag under argon. The following allylic halides were prepared by the procedures given in the literature cited: 3-bromocyclohexene,[144] 3-bromocycloheptene,[144] 3-bromocyclooctene,[144] 3-chlorocyclohexene,[145] (3-bromo-1-propenyl)benzene,[146] (3-chloro-1-propenyl)benzene,[147] (*E*)-5-chloro-1,3-pentadiene,[148] (*E*)-4-chloro-2-pentene,[149] 1-bromo-3-methyl-2-butene,[150] and 1-bromo-2-hexyne (**33**).[151] (*E*)-1-Bromo-2-hexene was prepared from commercial (Aldrich) (*E*)-hex-2-en-1-ol by a literature procedure.[152] (*Z*)-1-Bromo-2-hexene was prepared by the

same procedure,[152] from (Z)-hex-2-en-1-ol.[153] (Bromomethyl)benzene and 3-chloro-2-methyl-1-propene (**31**) were commercial (Aldrich) samples. All allylic halides were stored at 0°C and freshly distilled just before use.

Preparation of the Tellurium Reagent, Te^{2-}. The apparatus consisted of a 25 mL round bottomed flask to which were fused a condenser and side arm. The flask contained a Teflon coated magnetic stirring bar and the condenser was connected via a vacuum take-off to a vacuum / argon line. The side arm was closed using a rubber septum or, for those reactions which required long periods of reflux (greater than 3 h), a stopcock fitted with a rubber septum. The apparatus was oven dried overnight (120°C), assembled hot, charged immediately with commercial tellurium powder (*ca.* 200 mesh) (255 mg, 2.00 mmol) and evacuated (oil pump) while being allowed to cool. The apparatus was then filled with argon and purged of air by three cycles of oil pump evacuation and refilling with argon. Super-Hydride (1 M, 5.2 mL, 5.2 mmol) was then added by syringe and the mixture was stirred at room temperature for 5-7 h,* during which time a gas was evolved and the tellurium powder dissolved. The mixture became purple and then slowly faded to a very pale pink or off-white suspension. At this point, the reagent was ready for use. In those cases where it was let stand for longer periods, even under a positive pressure of argon, the reagent deteriorated, a crimson colour developed, and lower yields of coupled products were obtained.

Although this procedure has been described for a 2.00 mmol scale, it has also been used successfully to generate 1.00 mmol and 4.00 mmol batches of the tellurium reagent.

Coupling of 3-Bromocyclohexene. 3-Bromocyclohexene (322 mg, 2.00 mmol) in dry dioxane (2.0 mL plus 2.0 mL rinse) was added by syringe to the tellurium reagent (1.00 mmol), prepared as described above. The mixture was lowered into an oil bath pre-heated to 110°C and refluxed for 1 h. At this point, TLC (silica, hexane) analysis of the reaction mixture showed no further streaking of tellurium on the plate and so the reaction was

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*The length of time required for preparation of the Te^{2-} reagent could be shortened considerably by heating the mixture at reflux. In one experiment, the reagent was prepared in 45 minutes and gave completely satisfactory results in the coupling of 3-bromocyclohexene.

judged to be complete. The mixture was then cooled to room temperature and filtered with the aid of CH_2Cl_2 (*ca.* 100 mL) through a pad (2 x 2.5 cm) of Celite. The filtrate was concentrated to an oil, and partitioned between CH_2Cl_2 (50 mL) and water (50 mL). The aqueous phase was back-extracted with CH_2Cl_2 (2 x 25 mL) and the combined organic extracts were dried and concentrated to an oil. Chromatography over silica gel (60 x 1 cm) using hexane, followed by Kugelrohr distillation (110°C, 15 mm) gave **11**[55] (140 mg, 86%) as an apparently homogeneous (TLC, silica, hexane) oil of greater than 96% purity (VPC). NMR ($CDCl_3$, 100 MHz) δ 1.10-2.33 (m, 14H), 5.40-5.86 (m, 4H); ^{13}C NMR ($CDCl_3$, 22.6 MHz) δ 22.3, 25.5, 26.1, 40.2, 127.7, 128.0, 130.5, 130.7; exact mass, m/e 162.1406 (calcd for $C_{12}H_{18}$, m/e 162.1408).

Examination of the material by TLC (silica gel impregnated with 5% $AgNO_3$, 3:1 hexane-ethyl acetate) resolved the two diastereoisomeric components. Chromatography of a portion of the mixture (127 mg) over silica gel impregnated with 5% $AgNO_3$ (60 x 1 cm) using 4:1 hexane-ethyl acetate, gave the faster moving diastereoisomer (57 mg, 46% recovery) and the slower moving diastereoisomer (56 mg, 45% recovery). The more mobile material had NMR ($CDCl_3$, 100 Hz) δ 1.06-2.42 (m, 14H), 5.40-5.92 (m, 4H); ^{13}C NMR ($CDCl_3$, 22.6 MHz) δ 22.4, 25.5, 26.1, 40.2, 128.0, 130.7; exact mass, m/e, 162.1407 (calcd for $C_{12}H_{18}$, m/e 162.1408). The slower moving compound had NMR ($CDCl_3$, 100 MHz) δ 1.08-2.35 (m, 14H), 5.40-5.88 (m, 4H); ^{13}C NMR ($CDCl_3$, 22.6 MHz) δ 22.2, 25.4, 26.1, 40.1, 127.7, 130.4; exact mass, m/e 162.1413 (calcd for $C_{12}H_{18}$, m/e 162.1408).

Coupling of 3-Chlorocyclohexene. The procedure for 3-bromocyclohexene was followed exactly, using 3-chlorocyclohexene (234 mg, 2.00 mmol) to give the same diastereoisomeric mixture **11** (133 mg, 81%) of greater than 98% purity (VPC).

Coupling of 3-Bromocycloheptene. The procedure for 3-bromocyclohexene was followed exactly, using 3-bromocycloheptene (350 mg, 2.00 mmol) to give, after chromatography over silica gel (60 x 1 cm) using hexane and Kugelrohr distillation (165°C, 15 mm), **12**[154] (165 mg, 86%) as an apparently homogeneous (TLC, silica, hexane) oil of greater than 98% purity (VPC). Examination of the product by TLC (silica gel impregnated

with 5% $AgNO_3$, 3:1 hexane-ethyl acetate) partially resolved the two diastereoisomers. The mixture had NMR ($CDCl_3$, 100 MHz) δ 1.00-2.47(m, 18H), 5.42-5.97 (m, 4H); ^{13}C NMR ($CDCl_3$, 22.6 MHz) δ 27.0, 28.8, 30.6, 31.0, 31.3, 31.5, 45.5, 46.0, 131.5, 131.8, 136.3, 136.6; exact mass, m/e 190.1726 (calcd for $C_{14}H_{22}$, m/e 190.1721).

Coupling of 3-Bromocyclooctene. The procedure for 3-bromocyclohexene was followed exactly, using 3-bromocyclooctene (379 mg, 2.00 mmol) to give, after chromatography over silica gel (60 x 1 cm) using hexane and Kugelrohr distillation (180°C, 15 mm), **13**[154] (179 mg, 81%) as an apparently homogeneous (TLC, silica, hexane) oil of greater than 97% purity (VPC): NMR ($CDCl_3$, 100 MHz) δ 0.86-2.67 (m, 22H), 5.14-5.86 (m, 4H); ^{13}C NMR ($CDCl_3$, 22.6 MHz) δ 26.0, 26.8, 27.2, 29.6, 29.8, 34.3, 40.8, 41.1, 129.3, 129.4, 133.3, 134.5; exact mass, m/e 218.2037 (calcd for $C_{16}H_{26}$, m/e 218.2034).

Examination of the material by TLC (silica gel, impregnated with 5% $AgNO_3$, 3:1 hexane-ethyl acetate) resolved the two diastereoisomeric components. Chromatography of a portion of the mixture (107 mg) over silica gel impregnated with 5% $AgNO_3$ (60 x 1 cm) using 3:1 hexane-ethyl acetate gave, after Kugelrohr distillation (180°C, 15 mm), the faster moving isomer (52 mg, 49% recovery) as a white solid (mp 53-56°C) and the slower moving isomer (51 mg, 48% recovery) as a viscous oil of greater than 96% purity (VPC). The former had: NMR ($CDCl_3$, 100 MHz) δ 0.72-2.72 (m, 22H), 5.08-5.92 (m, 4H); ^{13}C NMR ($CDCl_3$, 22.6 MHz) δ 26.0, 26.8, 27.2, 29.8, 34.3, 41.1, 129.2, 134.4; exact mass, m/e 218.2036 (calcd for $C_{16}H_{26}$, m/e 218.2034). The latter had: NMR ($CDCl_3$, 100 MHz) δ 0.76-2.80 (m, 22H), 5.08-5.90(m, 4H); ^{13}C NMR ($CDCl_3$, 22.6 MHz) δ 25.9, 26.8, 27.2, 29.6, 34.3, 40.7, 129.4, 133.3; exact mass, m/e 218.2038 (calcd for $C_{16}H_{26}$, m/e 218.2034).

Coupling of (3-Bromo-1-propenyl)benzene. The procedure for 3-bromocyclohexene was followed exactly, using (3-bromo-1-propenyl)benzene (394 mg, 2.00 mmol) to give, after chromatography over silica gel (60 x 1 cm) using 99:1 hexane-ethyl acetate, a mixture of **14**,[126] **15**,[126] **16**,[126] and **17**[126] (215 mg, 91%) as an apparently homogeneous (TLC, silica, 95:5 hexane-ethyl acetate) oily, white solid. Examination of the product by TLC

(silica gel impregnated with 5% $AgNO_3$, 3:1 hexane-ethyl acetate) indicated a mixture of four isomers. An ^1H NMR spectrum (400 MHz) of the isomer mixture indicated that the products were present in the relative proportions (**16** and **17**). 15:14::1:3.9:3.0.

A portion of the mixture (211 mg) was crystallized from hexane to afford a sample of **14** (28 mg). The material from the mother liquors was then chromatographed over silica gel impregnated with 5% $AgNO_3$ (100 x 2 cm) using 5:1 hexane-ethyl acetate to give a further portion of **14** (44 mg). The combined samples of **14** (72 mg, 34% recovery) were recystallized twice from hexane [mp 77.5-79°C (lit.[126] mp 79.0-79.5°C)]. The chromatography also afforded **15** (77 mg, 36% recovery) as an oil, **16** (13 mg, 6% recovery) as a white solid (mp 77.5-86.5°C) after recrystallization from hexane (lit.[126] mp 86-87°C) and **17** (8 mg, 4% recovery) as an oil (lit.[126] mp 35-35.2°C). Compound **14** had: NMR ($CDCl_3$, 100 MHz) δ 2.16-2.58 (m, 4H), 6.04-6.60 (m, 4H), 6.92-7.52 (m, 10H); ^{13}C NMR ($CDCl_3$, 50.32 MHz) δ 32.9, 126.0, 126.9, 128.5, 129.9, 130.4, 137.7; exact mass, m/e 234.1411 (calcd for $C_{18}H_{18}$, m/e 234.1408). Compound **15** had: NMR ($CDCl_3$, 100 MHz) δ 2.49-2.79 (m, 2H), 3.26-3.58 (m, 1H), 4.89-5.19 (m, 2H), 5.80-6.50 (m, 3H), 6.80-7.60 (m, 10H); ^{13}C NMR ($CDCl_3$, 50.32 MHz) δ 39.0, 50.0, 114.6, 126.0, 126.3, 126.9, 127.7, 128.4, 131.4, 137.7, 141.4, 143.7; exact mass, m/e 234.1412 (calcd for $C_{18}H_{18}$, m/e 234.1408. Compound **16** had: NMR ($CDCl_3$, 100 MHz) δ 3.57-3.74 (m, 2H), 4.65-4.98 (m, 4H), 5.66-6.06 (m, 2H), 7.00-7.44 (m, 10H); ^{13}C NMR ($CDCl_3$, 100.64 MHz) δ 55.6, 115.8, 126.5, 128.4, 128.7, 140.2, 142.7; exact mass, m/e 234.1405 (calcd for $C_{18}H_{18}$, m/e 234.1408). Compound **17** had: NMR ($CDCl_3$, 100 MHz) δ 3.55-3.70 (m, 2H), 4.86-5.16 (m, 4H), 5.90-6.30 (m, 2H), 6.87-7.22 (m, 10H); ^{13}C NMR ($CDCl_3$, 50.32 MHz) δ 55.8, 115.8, 126.0, 128.1, 128.2, 140.5, 142.6; exact mass, m/e 234.1402 (calcd for $C_{18}H_{18}$, m/e 234.1408).

Coupling of (3-Chloro-1-propenyl)benzene. The procedure for (3-bromo-1-propenyl)benzene was followed exactly, using (3-chloro-1-propenyl)benzene (306 mg, 2.00 mmol) to give the same (^1H NMR, 400 MHz) isomer mixture of **14, 15, 16** and **17** (219 mg, 93%).

Coupling of (*E*)-5-Chloro-1, 3-pentadiene. (*E*)-5-Chloro-1, 3-pentadiene (205 mg, 2.00 mmol) in dry THF (2.0 mL plus 2.0 mL rinse) was added by syringe to the tellurium reagent (1.00 mmol) prepared as described previously. The mixture was lowered into an oil bath, pre-heated to 80°C and refluxed for 1 h. At this point, TLC (silica, hexane) analysis of the reaction mixture showed no further streaking of tellurium on the plate and so the reaction was judged to be complete. Analysis of the solution by VPC showed a mixture of **18**[154] (62 mg, 46%) and **19**[154] (48 mg, 36%).

To isolate samples of each isomer for characterization, the reaction was repeated on a larger scale (4.00 mmol of the tellurium reagent). After being refluxed for 1 h, the reaction mixture was cooled to room temperature, and filtered with the aid of CH_2Cl_2 (*ca.* 100 mL) through a pad (2 x 2.5 cm) of Celite. The filtrate was concentrated by distillation at atmospheric pressure through a Vigreux column (12 cm) to *ca.* 25 mL and was mixed with water (50 mL) and extracted with pentane (3 x 50 mL). The combined organic extracts were dried and concentrated (Vigreux column, 1 atmosphere) to a volume of *ca.* 2 mL. Chromatography over silica gel (30 x 1 cm) using pentane, concentration (Vigreux column, 1 atmosphere) and further chromatography over silica gel impregnated with 5% $AgNO_3$ (30 x 1 cm) using 3:2 pentane-ether effected separation of **18** and **19**. Concentration (Vigreux column, 1 atmosphere) and Kugelrohr distillation (100°C, 500 mm) gave homogeneous (TLC, silica, hexane; TLC, silica gel impregnated with 5% $AgNO_3$, ether) samples of **18**, of greater than 97% purity (VPC) and **19**, of greater than 93% purity (VPC), the major contaminant in the latter being **18** (4%). Compound **18** had: NMR ($CDCl_3$, 100 MHz) δ 2.02-2.40 (m, 4H), 4.81-5.30 (m, 4H), 5.51-6.74 (m, 6H); ^{13}C NMR ($CDCl_3$, 22.6 MHz) δ 32.2, 115.0, 131.5, 134.2, 137.2; exact mass, m/e 134.1095 (calcd for $C_{10}H_{14}$, m/e 134.1096). Compound **19** had: NMR ($CDCl_3$, 100 MHz) δ 2.10-2.45 (m, 2H), 2.63-3.00 (m, 1H), 4.86-5.28 (m, 6H), 5.46-6.54 (m, 5H); ^{13}C NMR ($CDCl_3$, 22.6 MHz) δ 37.6, 47.6, 114.7, 115.2, 132.5, 137.1, 140.4; exact mass, m/e 134.1087 (calcd for $C_{10}H_{14}$, m/e 134.1096).

Coupling of (*E*)-4-Chloro-2-pentene. (*E*)-4-Chloro-2-pentene* (419 mg, 4.00 mmol) in dry dioxane (4.0 mL plus 4.0 mL rinse) was added by syringe to the tellurium reagent (2.00

*This compound contained *ca.* 10% of the other double bond isomer, as estimated by ^{13}C NMR spectroscopy.

mmol) prepared as described previously. The mixture was lowered into an oil bath, pre-heated to 110°C and refluxed for 1 h. Analysis of the solution by VPC showed the presence of **20**[154] (228 mg 82%).

In order to isolate a sample of the product, the reaction was repeated exactly as above. After being refluxed for 1 h, the mixture was cooled to room temperature and filtered with the aid of CH_2Cl_2 (*ca.* 100 mL) through a pad (2 x 2.5 cm) of Celite. The filtrate was concentrated by distillation at atmospheric pressure through a Vigreux column (12 cm) to *ca.* 5 mL and partitioned between pentane (50 mL) and water (50 mL). The aqueous phase was washed with pentane (2 x 25 mL) and the combined pentane extracts were dried and concentrated (Vigreux column, 1 atmosphere) to an oil. Chromatography over silica gel (60 x 1 cm) using pentane, concentration (Vigreux column, 1 atmosphere) and Kugelrohr distillation (70°C, 12 mm) gave **20**[154] as an apparently homogeneous (TLC, silica, hexane) oil of greater than 99% purity (VPC). Analysis of the product by TLC (silica gel impregnated with 5% $AgNO_3$, 3:1 hexane-ethyl acetate) indicated a mixture of at least three isomers. The product had: IR (film) 965 cm^{-1} (strong), 720 cm^{-1}(weak); NMR ($CDCl_3$, 100 MHz) δ 0.72-1.14 (m, 6H), 1.47-2.54 (m, 8H), 5.03-5.62 (m, 4H); ^{13}C NMR ($CDCl_3$, 22.6 MHz) δ 13.1, 17.5, 18.0, 18.3, 18.6, 36.5, 41.9, 42.4, 42.8, 122.5, 122.8, 123.7, 123.9, 134.9, 135.1, 136.0; exact mass, m/e 138.1408 (calcd for $C_{10}H_{18}$, m/e 138.1408).

Coupling of 1-Bromo-3-methyl-2-butene. 1-Bromo-3-methyl-2-butene (596 mg, 4.00 mmol) in dry dioxane (2.0 mL plus 2.0 mL rinse) was added by syringe to the tellurium reagent (2.00 mmol) prepared as described previously. The mixture was lowered into an oil bath, pre-heated to 110°C, and refluxed for 3 h.* Analysis of the solution by VPC showed a mixture of **21**[155] (120 mg, 43%) and **22**[155] plus **23**[155] (83 mg, 30%).

In order to isolate samples of each isomer for identification, the reaction was repeated on a larger scale (4.00 mmol of the tellurium reagent). After being refluxed for 3 h, the mixture was cooled to room temperature and filtered with the aid of CH_2Cl_2 (*ca.* 150 mL) through a pad (2 x 2.5 cm) of Celite. The filtrate was concentrated by distillation at atmospheric pressure through a Vigreux column (12 cm) to *ca.* 50 mL and partitioned

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*Analysis of the reaction mixture by TLC (silica, hexane) after 1 and 2 h, still showed streaking of tellurium on the plate.

between water (250 mL) and pentane (4 x 75 mL). The combined pentane extracts were dried and concentrated (Vigreux column, 1 atmosphere) to *ca.* 2 mL. Chromatography over silica gel (60 x 1 cm) using pentane and concentration (Vigreux column, 1 atmosphere) gave an oil, which was chromatographed over silica gel impregnated with 5% $AgNO_3$ (60 x 1 cm) using 9:1 pentane-ether. Concentration (Vigreux column, 1 atmosphere) and Kugelrohr distillation (120°C, 90 mm), gave homogeneous (TLC, silica, hexane; TLC, silica gel impregnated with 5% $AgNO_3$, 9:1 pentane-ether) samples of **21** (100% pure by VPC), **22** (greater than 98% pure by VPC) and **23** (100% pure by VPC). Compound **21** had: NMR ($CDCl_3$, 100 MHz) δ 1.61 (s, 6H), 1.69 (s, 6H), 1.86-2.12 (m, 4H), 4.97-5.28 (m, 2H); ^{13}C NMR ($CDCl_3$, 22.6 MHz) δ 17.7, 25.7, 28.4, 124.5, 131.5; exact mass, m/e 138.1408 (calcd for $C_{10}H_{18}$, m/e 138.1408). Compound **22** had: NMR ($CDCl_3$, 100 MHz) δ 0.99 (s, 6H), 1.61 (s, 3H), 1.73 (d, J = 1.4 Hz, 3H), 1.98 (d, J = 7.4 Hz, 2H), 4.78-5.02 (m, 2H), 5.14 (t m, J = 7.4, 1.4 Hz, 1H), 5.66-6.02 (m, 1H); ^{13}C NMR ($CDCl_3$, 22.6 MHz) δ 17.9, 25.9, 26.5, 37.4, 40.8, 110.0, 121.2, 132.8, 148.7; exact mass, m/e 138.1409 (calcd for $C_{10}H_{18}$, m/e 138.1408). Compound **23** had:NMR ($CDCl_3$, 100 MHz) δ 0.99 (s, 12H), 4.78-5.06 (m, 4H), 5.78-6.14 (m, 2H); ^{13}C NMR ($CDCl_3$, 22.6 MHz) δ 22.5, 41.3, 111.7, 146.2; exact mass, m/e 138.1405 (calcd for $C_{20}H_{18}$, m/e 138.1408).

Coupling of (*E*)-1-Bromo-2-hexene. The procedure for 3-bromocyclohexene was followed using (*E*)-1-bromo-2-hexene* (327 mg, 2.00 mmol) and a reflux period of 21 h.** Chromatography over silica gel (60 x 1 cm) using hexane, and Kugelrohr distillation (100°C, 13 mm) gave an apparently homogeneous (TLC, silica, hexane) oil (100 mg, 60%), judged to be a mixture of isomers by VPC (three peaks: 5.94%, 39.49% and 54.25%). TLC (silica gel impregnated with 5% $AgNO_3$, 9:1 hexane-ethyl acetate) resolved four components.

To obtain a sample of each component for characterization, the reaction was repeated on a larger scale (4.00 mmol of the tellurium reagent). Chromatography over

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*This compound contained *ca.* 10% of the other double bond isomer, as estimated by ^{13}C NMR spectroscopy.

**Even after 21 h at reflux, some streaking of tellurium was noticed when the reaction mixture was analysed by TLC (silica, hexane). Furthermore, when the reaction mixture was chromatographed, some tellurium was deposited as the mixture moved down the column.

silica gel (60 x 1 cm) using hexane, afforded a homogeneous (TLC, silica, hexane) clear, colourless oil (433 mg, 65%). Chromatography of this isomer mixture over silica gel impregnated with 5% $AgNO_3$ [twice (70 x 2 cm) using 19:1 hexane-ethyl acetate, once (70 x 2 cm) using 97:3 hexane-ethyl acetate and once (30 x 0.5 cm) using 97:3 hexane-ethyl acetate] gave four fractions which were each rechromatographed over silica gel (15 x 1.5 cm) using hexane. Kugelrohr distillation of each fraction gave material that was homogeneous by TLC (silica, hexane, silica gel impregnated with 5% $AgNO_3$, 9:1 hexane-ethyl acetate).

The least polar fraction (59.1 mg, 13% recovery, bp 120°C, 20 mm) was **24**[156] of greater than 97% purity (VPC), and had: IR (film) 970 cm^{-1} (strong); NMR ($CDCl_3$, 100 MHz) δ 0.89 (t, J = 7 Hz, 6H), 1.17-1.58 (m, 4H), 1.80-2.16 (m, 8H), 5.30-5.51 (m, 4H); ^{13}C NMR ($CDCl_3$, 22.6 MHz) δ 13.6, 22.7, 32.8, 34.7, 130.0, 130.5; exact mass, m/e 166.1723 (calcd for $C_{12}H_{22}$, m/e 166.1721).

The second fastest fraction (61.8 mg, 14% recovery, bp 130°C, 20 mm) was **25**[156] of greater than 92% purity (VPC), and had: IR (film) 970 cm^{-1} (strong), 720 cm^{-1} (weak); NMR ($CDCl_3$, 100 MHz) δ 0.85 and 0.86 (2 overlapping triplets, J = 7 Hz, 6H), 1.13-1.56 (m, 4H), 1.78-2.20 (m, 8H), 5.22-5.46 (m, 4H); ^{13}C NMR ($CDCl_3$, 22.6 MHz) δ 13.7, 22.7, 22.9, 27.5, 29.4, 32.8, 34.8, 129.4, 130.0, 130.6; exact mass, m/e 166.1720 (calcd for $C_{12}H_{22}$, m/e 166.1721).

The third fastest fraction (87.5 mg, 20% recovery, bp 130°C, 20 mm) was made up of three components as judged by VPC: **26** (66.48%), **27**[156] (23.14%) and **28** (10.06%). The mixture had: IR (film) 1000 cm^{-1} (moderate), 970 cm^{-1} (strong), 915 cm^{-1} (strong), 745 cm^{-1} (weak); NMR ($CDCl_3$, 100 MHz) δ 0.73-1.04 (m, 5.8H), 1.08-1.59 (m, 5.8H), 1.78-2.20 (m, 5.4H), 4.77-5.07 (m, 1.9H), 5.26-5.79 (m, 3.2H); ^{13}C NMR ($CDCl_3$, 22.6 MHz) displayed signals corresponding to **26** at δ 14.1, 20.2, 22.8, 34.8, 36.4, 38.3, 43.9, 113.8, 128.4, 131.6, 143.1; signals corresponding to **27** at δ 13.6, 22.9, 27.5, 29.4, 129.4, 130.1; and signals corresponding to **28** at δ 13.8, 20.5, 34.0, 48.6, 115.0, 141.8; the mixture had exact mass, m/e 166.1721 (calcd for $C_{12}H_{22}$, m/e 166.1721).

The most polar fraction (35.4 mg, 8% recovery, bp 135°C, 20 mm) was made up of two components as judged by VPC: **29** (78.48%) and **28** (21.05%). This mixture had: IR (film) 995 cm^{-1} (moderate), 915 cm^{-1} (strong), 745 cm^{-1} (very weak); NMR ($CDCl_3$, 100

MHz) δ 0.78-1.04 (m, 5.3H), 1.15-1.62 (m, 6.8H), 1.85-2.30 (m, 4.6H), 4.80-5.14 (m, 2.3H), 5.30-5.82 (m, 2.9H); ^{13}C NMR ($CDCl_3$, 22.6 MHz) displayed signals corresponding to **29** at δ 14.2, 20.3, 22.9, 29.5, 32.7, 36.6, 44.0, 113.9, 128.0, 130.5, 143.1, and signals corresponding to **28** at δ 13.8, 20.5, 35.0, 48.0, 115.3, 140.3, the mixture had exact mass, m / e 166.1722 (calcd for $C_{12}H_{22}$, m / e 166.1721).

Coupling of (*Z*)-1-Bromo-2-hexene. The procedure for (*E*)-1-bromo-2-hexene was followed, except on a larger scale (2.00 mol of the tellurium reagent) using (*Z*)-1-bromo-2-hexene* (653 mg, 4.00 mmol). Chromatography over silica gel (60 x 1 cm) using hexane, and Kugelrohr distillation (110°C, 13 mm) gave the same product mixture (177 mg, 53%) (VPC, TLC, IR, ^{1}H and ^{13}C NMR and MS) as that obtained from (*E*)-1-bromo-2-hexene.

Coupling of (Bromomethyl)benzene.

a) (Bromomethyl)benzene (684 mg, 4.00 mmol) in dry dioxane (4.0 mL plus 4.0 mL rinse) was added by syringe to the tellurium reagent (2.00 mmol) prepared as described previously. The mixture was lowered into an oil bath, pre-heated to 110°C and refluxed for a total of 48 h. No tellurium was deposited and analysis of the reaction mixture by TLC / (silica, 49:1 hexane-ethyl acetate) showed no starting bromide, or 1,1'-(1, 2-ethanediyl)bisbenzene (**30**), by comparison with an authentic sample.

b) A thick walled ampoule (volume *ca.* 25 mL) was oven-dried overnight (120°C), charged with tellurium powder (*ca.* 200 mesh) (255mg, 2.00 mmol), closed with a rubber septum and purged of all air by three cycles of oil pump evacuation, and refilling with argon (by means of a needle, passing through the septum). Super-Hydride (1 M, 5.2 mL, 5.2 mmol) was injected and the mixture was lowered into a sonic bath (used instead of magnetic stirring) and heated to *ca.* 70°C. After 45 min, all of the tellurium had dissolved and the mixture had become a milky white suspension. (Bromomethyl)benzene (685 mg, 4.00 mmol) in dry dioxane (4.0 mL plus 4.0 mL rinse) was added. The ampoule was sealed, and heated in an oil bath at 160°C for 3 h. The mixture was cooled to room temperature and filtered with the aid of CH_2Cl_2 (*ca.* 100 mL), through a pad (2 x 2.5 cm) of

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*This compound contained *ca.* 10% of the other double bond isomer as estimated by ^{13}C NMR spectroscopy.

Celite. The filtrate* was concentrated to an oil, and partitioned between CH_2Cl_2 (50 mL) and water (50 mL). The aqueous phase was back-extracted with CH_2Cl_2 (2 x 25 mL) and the combined organic extracts were dried and concentrated to an oil.. Chromatography** over silica gel (60 x 1 cm) using 49:1 hexane-ethyl acetate and again (60 x 1 cm) using hexane, followed by Kugelrohr distillation (110°C, 0.25 mm) gave **30**[157] (136 mg, 37%) as a white solid, homogeneous by TLC (silica, 49:1 hexane-ethyl acetate), mp 45-50°C (lit.[157] mp 52°C); NMR ($CDCl_3$, 100 MHz) δ 2.90 (s, 4H), 7.02-7.38 (m, 10H); ^{13}C NMR ($CDCl_3$, 22.6 MHz) δ 37.9, 125.9, 128.4, 128.5, 141.8; exact mass, m/e 182.1093 (calcd for $C_{14}H_{14}$, m/e 182.1096).

Attempted Coupling of 3-Chloro-2-methyl-1-propene (31). 3-Chloro-2-methyl-1-propene (**31**) (362 mg, 4.00 mmol) in dry dioxane (4.0 mL plus 4.0 mL rinse) was added by syringe to the tellurium reagent (2.00 mmol), prepared as described previously. The reaction mixture was lowered into an oil bath, pre-heated to 110°C and refluxed for 50h. At this stage, little tellurium had been deposited, and analysis of the mixture by TLC (silica, hexane) showed considerable streaking of tellurium on the plate. No attempt was made to isolate hydrocarbon products from this reaction mixture.

Preparation of 1-(Chloromethyl)-4-(1-methylethenyl)-1-cyclohexene (32). The general procedure of reference 158 was used. 4-(1-Methylethenyl)-1-cyclohexene-1-methanol (20.00 g, 0.13 mol) and dry HMPA (45 mL, 46 g, 0.26 mol) were dissoved in anhydrous ether (130 mL) under nitrogen. The solution was cooled to 0°C and a solution of methyllithium in ether (1.8 M, 73 mL, 0.13 mol) was added over 45 min with mechanical stirring. A solution of 4-methylbenzenesulfonyl chloride (25 g, 0.13 mol) in ether (130 mL) was added over 30 min. Dry lithium chloride (5.57 g, 0.13 mol) was added in one portion and the stirred mixture was allowed to come to room temperature overnight. Ether (100 mL) and water (100 mL) were added, the layers were separated, and the ether phase was extracted with water (4 x 100 mL) and then with saturated sodium chloride (100 mL). The ether solution was dried and evaporated to an oil which was distilled

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*Tellurium was deposited during workup.
**Tellurium was deposited all the way down the column.

through a 20 cm Vigreux column. The fraction boiling at 67.5°C. (0.7 mm) was collected, but contained a small amount of polar material (TLC, silica, 9:1 hexane-ethyl acetate). Chromatography over silica gel (8 x 2.5 cm) using hexane and redistillation as before, gave **32** (12.81 g, 0.075 mol, 57%) as an apparently homogeneous (TLC, silica, 9:1 hexane-ethyl acetate) liquid which had: NMR ($CDCl_3$, 100 MHz) δ 1.20-2.54 (m, 10H containing a singlet at δ 1.75), 4.00 (s, 2H), 4.72 (m, 2H), 5.87 (m, 1H); ^{13}C NMR ($CDCl_3$, 15.08 MHz) δ 149.4 (s), 134.2 (s), 127.0 (d), 109.0 (t), 50.1 (t), 40.7 (s), 30.7 (t), 27.4 (t), 26.4 (t), 20.7 (q); exact mass, m/e 172.0834 calcd for $C_{10}H_{15}{}^{37}Cl$, m/e 172.0833), m/e 170.0858 (calcd for $C_{10}H_{15}{}^{35}Cl$, m/e 170.0863). Anal. Calcd for $C_{10}H_{15}Cl$: C, 70.37; H, 8.86. Found: C, 70.55; H, 8.88.

Attempted Coupling of 1-(Chloromethyl)-4-(1-methylethenyl)-1-cyclohexene (32). Compound **32** (341 mg, 2.00 mmol) in dry dioxane (2.0 mL plus 2.0 mL rinse) was added by syringe to the tellurium reagent (1.00 mmol) prepared as described previously. The reaction mixture was lowered into an oil bath, pre-heated to 110°C and refluxed for 48 h. Workup in the usual manner produced a dark yellow, malodorous oil which deposited tellurium on standing and upon attempted column chromatography. Attempts to isolate pure hydrocarbon products were unpromising.

Attempted Coupling of 1-Bromo-2-hexyne (33). 1-Bromo-2-hexyne (**33**) (323 mg, 2.00 mmol) in dry dioxane (2.0 mL plus 2.0 mL rinse) was added by syringe to the tellurium reagent (1.00 mmol), prepared in the usual manner. The mixture was lowered into an oil bath, pre-heated to 110°C and refluxed for 43 h. Almost no tellurium was deposited and attempts to isolate hydrocarbon products were unsuccessful.

Coupling of 3-Bromocyclohexene Using Commercial Li_2Te.

a) Without Triethylborane. A solution of 3-bromocyclohexene (3.16 mg, 1.96 mmol) in dry dioxane (2.0 mL plus 2.0 mL rinse) was added to a stirred suspension of commercial lithium telluride (139 mg, 0.981 mmol) in dry THF (3.0 mL). The mixture was stirred for 30 min at room temperature and was then lowered into an oil bath pre-heated

to 110°C and refluxed for 2 h. Workup,* chromatography, and Kugelrohr distillation as previously described for the coupling of 3-bromocyclohexene, gave **11** (62.3 mg, 0.384 mmol, 39%) as an apparently homogeneous (TLC, silica, hexane) oil of greater than 99% purity (VPC).

b) With Triethylborane. This experiment was performed as described for a) above except that triethylborane (0.460 mL, 320 mg, 3.27 mmol) was added to the suspension of lithium telluride (178 mg, 1.26 mmol) in dry THF (4.0 mL) before the addition of 3-bromocyclohexene (405 mg, 2.51 mmol). Workup,* chromatography, and Kugelrohr distillation as before gave **11** (59.0 mg, 0.364 mmol, 28%) as an apparently homogeneous (TLC, silica, hexane) oil of greater than 99% purity (VPC).

Detection of Bis(2-cyclohexenyl)telluride (36) by ^{13}C NMR. 3-Bromocyclohexene (644 mg, 4.00 mmol) in dry THF (4.0 mL plus 4.0 mL rinse) was added to the tellurium reagent (2.00 mmol) prepared in the usual manner, in a septum stoppered centrifuge tube. The tube contained a magnetic stirring bar and was filled with argon. The mixture was stirred at room temperature for 15 min,** and then centrifuged for 10 min to remove a small amount of particulate matter. A portion of the supernatant (2.0 mL) was transferred to a septum stoppered, argon filled NMR tube. THF-d_8 (1.0 mL) was added and the ^{13}C NMR spectrum of the mixture was recorded (22.6 MHz). The diagnostically significant features of the spectrum were resonances at δ 125.8, 125.9, 130.6 and 130.7, and the absence of resonances between δ 30.0 and 65.0. The NMR sample remained unchanged on standing under argon for longer than ten days. However, upon exposure to air, the mixture rapidly deposited black tellurium. ^{13}C NMR spectra were also recorded for 3-bromocyclohexene and 2,2'-bicyclohexenyl (**11**) in the presence of one and two equivalents respectively, of triethylborane. The former had: ^{13}C NMR (THF-d_8, 22.6 MHz) δ 19.5, 25.4, 33.7, 49.1, 130.0 and 131.2.*** The latter had ^{13}C NMR (THF-d_8, 22.6

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*A small amount of tellurium was deposited during workup.
This delay period has no substantive effect on the coupling reaction as was shown by the following experiment: 3-Bromocyclohexene (644 mg, 4.00 mmol) in dry THF (4.0 mL plus 4.0 mL rinse) was added to the tellurium reagent (2.00 mmol) prepared as described previously. The solution was stirred at room temperature for 1 h, and was then diluted with dioxane (20 mL). The coupling reaction was completed as desribed previously for 3-bromocyclohexene to give **11 (265 mg, 1.63 mmol, 81%) of greater than 99% purity as judged by VPC.
***Signals due to triethylborane are not reported.

MHz) δ 23.2, 26.2, 26.8, 41.2, 128.2, 128.6, 131.2, 131.3.

Attempted ESR Detection of Radicals During the Formation of Bisallylic Telluride (36). A suspension of the tellurium reagent (1.00 mmol), prepared as described previously, and a solution of 3-bromocyclohexene (322 mg, 2.00 mmol) in dry THF (2.0 mL) were mixed in an ESR flow reaction vessel under argon by slow, simultaneous addition from two syringes. No ESR signal was observed.

Attempted ESR Detection of Radicals During the Decomposition of Bisallylic Telluride (36). The tellurium reagent (2.00 mmol) was prepared as described previously, except in a septum sealed centrifuge tube. 3-Bromocyclohexene (644 mg, 4.00 mmol) in dry dioxane (4.0 mL plus 4.0 mL rinse) was added by syringe. The mixture was stirred at room temperature for 10 min, and was then centrifuged for 10 min to remove any particulate matter. A small portion of the solution was transferred by syringe to a septum sealed, argon flushed quartz tube. The tube was placed in a variable temperature ESR probe and heated to 100°C. No ESR signal was detected even though the solution went from clear yellow, to brown with a black (tellurium) precipitate.

Cross Coupling of 3-Bromocyclohexene and 3-Bromocycloheptene. 3-Bromocyclohexene (644 mg, 4.00 mmol) in dry THF (4.0 mL plus 4.0 mL rinse) was added to the tellurium reagent (2.00 mmol), prepared as described previously. 3-Bromocycloheptene (701 mg, 4.00 mmol) in dry THF (4.0 mL plus 4.0 mL rinse) was added to another sample of the tellurium reagent (2.00 mmol). These solutions were stirred at room temperature for 30 min, and then aliquots (3.0 mL) of each were mixed, diluted with dioxane (9.2 mL) and lowered into an oil bath pre-heated to 110°C. The reaction mixture was refluxed for 1 h. Workup in the usual fashion followed by column chromatography over silica gel (60 x 1 cm) using hexane, and then Kugelrohr distillation (145-170°C, 17 mm) gave 107 mg of a clear, colourless, apparently homogeneous (TLC, silica, hexane) oil. VPC analysis showed the product to be greater than 98% pure and to consist of three resolvable components in a ratio of 1:1.3:1. The first and third peaks had retention times corresponding to 2,2'-bicyclohexenyl (**11**) and 2,2'-bicycloheptenyl (**12**), respectively.

Examination of the material by VPC/MS showed the three peaks to display molecular ions of m/e 162, 176, and 190, respectively.

Coupling of (3-Chloro-1-propenyl)benzene using Te_2^{2-}. The procedure used previously for the coupling of (3-chloro-1-propenyl)benzene was followed, except that the tellurium reagent was prepared with different proportions of Super-Hydride (1 M, 2.6 mL, 2.6 mmol) and tellurium powder (255 mg, 2.00 mmol). After a stirring period at room temperature of 6 h all the tellurium had dissolved, and the mixture was dark crimson. (3-Chloro-1-propenyl)benzene (306 mg, 2.00 mmol) in dry dioxane (2.0 mL plus 2.0 mL rinse) was added, causing an immediate deposition of tellurium. The mixture was lowered into an oil bath, pre-heated to 110°C, and refluxed for 1 h. During this period, further deposition of tellurium was observed. Workup as before, followed by chromatography over silica gel (60 x 1 cm) using 99:1 hexane-ethyl acetate gave the same (^{1}H NMR, 400 MHz) isomer ratio of **14**, **15**, **16**, and **17** (207 mg, 88%) as obtained by the previous couplings of (3-chloro-1-propenyl)benzene and (3-bromo-1-propenyl)benzene.

Attempted Coupling of 3-Bromocyclohexene using Se_2^{2-}. A suspension of lithium selenide in THF was prepared by the literature procedure.[122] Under argon, grey selenium powder (158 mg, 2.00 mmol) was added portionwise to Super-Hydride (1 M, 4.2 mL, 4.2 mmol) with magnetic stirring. The milky, white suspension was stirred for a further 20 min, then 3-bromocyclohexene (645 mg, 4.00 mmol) and dry *tert*-butyl alcohol** (0.37 mL, 0.29 g, 3.9 mmol) in dry dioxane (4.0 mL plus 4.0 mL rinse) were added by syringe. Within 1 h all of the halide had reacted (TLC). After a further 2.5 h at room temperature, the mixture was lowered into an oil bath (110°C) and refluxed for 3.5 h. No metallic selenium was deposited, and VPC analysis of the reaction mixture indicated less than a 2% yield of the coupled product **11**.

In a preparative experiment,* grey selenium powder (154 mg, 1.95 mmoL) was added portionwise under nitrogen to Super-Hydride (1 M, 4.0 mL, 4.0 mmol). After the mixture had been stirred for 20 min, 3-bromocyclohexene (647 mg, 4.02 mmol) and dry *tert*-butyl alcohol** (0.37 mL, 0.29 g, 3.9 mmol) in dry THF (4.0 mL plus 2.0 mL rinse) was

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*This experiment was performed by N. Moss.
***tert*-Butyl alcohol was found to have no effect on the tellurium reaction.

added by syringe. After 3 h of stirring at room temperature, the reaction was complete (TLC) and the mixture was taken up in ether (40 mL) and washed with water (3 x 20 mL). The combined aqueous extracts were back extracted with ether (30 mL). The combined ether extracts were dried (Na_2SO_4) and concentrated to an oily solid. The crude product was chromatographed over silica gel (40 x 1.5 cm) using 9 1 hexane-ethyl acetate, then again over silica gel (66 x 1.5 cm) using hexane, to give **38** (306 mg, 65%) as a homogeneous (TLC, silica, 9 1 hexane-ethyl acetate) oil. Compound **38** had NMR ($CDCl_3$, 100 MHz) δ 1.31-2.31 (m, 12H), 3.52-3.77 (m, 2H), 5.52-5.96 (m, 4H). ^{13}C NMR ($CDCl_3$, 22.6 MHz) δ 20.0, 20.1, 24.9, 30.7, 31.0, 36.6, 128.4, 128.6, 128.9, 129.0; exact mass, m/e 242.0571 (calcd for $C_{12}H_{18}Se$, m/e 242.0574). A satisfactory combustion analysis could not be obtained for this compound.

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V. APPENDIX

The following equations were used to calculate ^{13}C NMR chemical shifts for compounds **24** to **29**

For acyclic, sp^3 carbon atoms, the chemical shift of a particular carbon atom is given by the equation[159]

$$\delta C = Bs + \sum_{m=2}^{4} DmAsm + \gamma s N_3 + \Delta s N_4$$

where s is the number of carbon atoms bonded to the carbon in question; Bs, Asm, γs and Δs are constants (given below); N_3 and N_4 are the number of carbon atoms 3 and 4 bonds away from the carbon atom in question, Dm is the number of carbon atoms bonded to the carbon in question which have m attached carbon atoms (including the carbon atom in question).

Constants

B_1	6.8	B_2	15.34	B_3	23.46	B_4	27.77
A_{12}	9.56	A_{22}	9.75	A_{32}	6.60	A_{42}	2.26
A_{13}	17.83	A_{23}	16.70	A_{33}	11.14	A_{43}	3.96
A_{14}	25.48	A_{24}	21.43	A_{34}	14.70	A_{44}	7.35
γ_1	-2.99	γ_2	-2.69	γ_3	-2.07	γ_4	0.68
Δ_1	0.49	Δ_2	0.25				

For sp^2 carbon atoms the chemical shift of a particular carbon atom is given by the equation[160]

$$C = 123.3 + n\alpha + n\beta + n\gamma + n\alpha' + n\beta' + n\gamma'$$

where nx is the number of carbon atoms in the x position and α, β, γ, α', β' and γ' are constants, given below.

Constants

α	10.6	α'	7.9
β	7.2	β'	-1.8
γ	-1.5	γ'	1.5

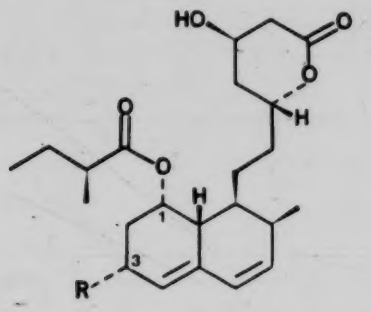
The following adjustments to calculated chemical shifts were also made: For alkenes with *cis*-stereochemistry, 1.1 ppm was subtracted from the calculated chemical shift of the sp^2 carbon atoms,[160] and 6 ppm was subtracted from the calculated chemical shift of the α carbon atoms.[161]

CHAPTER 2

SYNTHETIC STUDIES RELATED TO MEVINOLIN AND COMPACTIN

I. INTRODUCTION

The fungal metabolites Mevinolin (1)* and Compactin (2)** have a wide range of biological activities and are the subject of considerable patent and journal literature. For example, Mevinolin is fungicidal[1-5] and it inhibits elongation of the roots in etiolated radish[6-8] and wheat seedlings.[7] Compactin inhibits the growth of plant callus[3] and the production of Juvenile hormone in some insects,[9,10] and it induces abnormal gastrulation in sea urchin embryos.[11] Both Mevinolin and Compactin prevent gallstones in hamsters[12] and act as neoplasm inhibitors.[13] Interest in these compounds, however, is due largely to the fact that they significantly lower blood cholesterol levels in many mammals,[1,14-16] most importantly, in man.[17,18]



1 R=CH_3
2 R=H

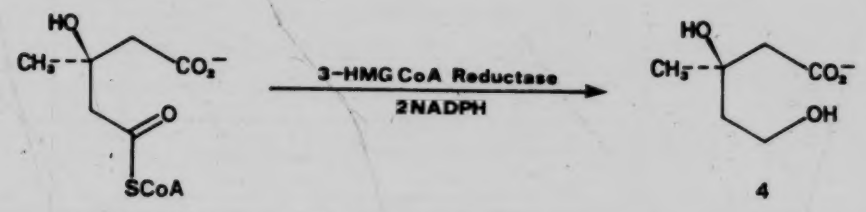
Heart disease is the major cause of death in western societies.[1] In the United States, for example, it accounted for 38% of all deaths in 1981.[19] While heart disease is actually a wide variety of diseases, the major cause of many is atherosclerosis, or the build up of fatty deposits on the inner walls of arteries.[19] A significant risk factor for atherosclerosis, and therefore, a factor implicated in the occurrence of heart disease, is an elevated level of cholesterol in blood.[20] Clearly, compounds which lower blood cholesterol levels are of considerable importance in the study of heart disease.

---

*Mevinolin, isolated from *Aspergillus terreus*,[1] appears to be identical to Monakolin K, isolated from *Monascus ruber*.[2]

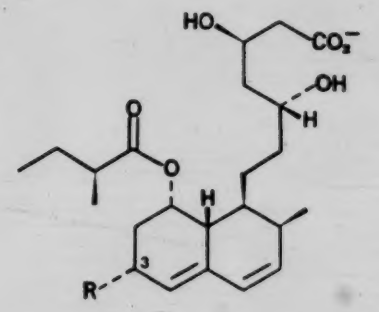
**Compactin and ML-236B, isolated almost simultaneously from *Penicillium brevicompactum*[3] and *Penicillium citrinum*[4] respectively, appear to be identical metabolites.

In the human body, more than 50% of the total cholesterol originates from *de novo* biosynthesis.[21] This process, therefore, represents an obvious target for control of blood cholesterol levels. Mevinolin and Compactin are thought to act by a reversible, competitive inhibition of the enzyme 3-hydroxy-3-methylglutaryl coenzyme A reductase.[22] This enzyme is responsible for mediating the rate limiting step in cholesterol biosynthesis, namely, the two stage reduction of 3-hydroxy-3-methylglutaryl coenzyme A (**3**) to mevalonate (**4**) (equation 1).[23]



3 **4** (1)

The active forms of Mevinolin and Compactin are thought to be the lactone ring opened dihydroxy acids **5**.[1,24] They may be effective because of the close resemblance of the upper portion of these molecules to both the natural substrate (**3**) and the product (**4**) of the enzymatic reduction.

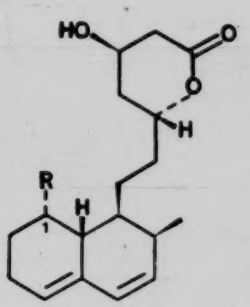


5

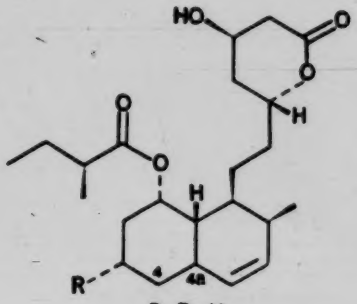
However, it is not only the lactone unit which is important, since simply replacing the C-3 methyl group of Mevinolin with a hydrogen (as in Compactin) results in a 3 to 5 fold decrease in activity.[1,26] Clearly, it would be valuable to have analogues of these compounds available, both to assess the effect of various structural features on biological

activity, and also to explore the possibility of designing a clinically useful drug to treat hypercholesterolemia.

A number of analogues of Mevinolin and Compactin are available by fermentation. For example, ML-236A (**6**),[26] ML-236C (**7**)[26] and 4,4a-dihydrocompactin (**8**)[27] are cometabolites of Compactin, while 4,4a-dihydromevinolin (**9**) has been isolated along with Mevinolin.[23] All of these compounds show attenuated hypocholesterolemic activity compared to Mevinolin or Compactin.



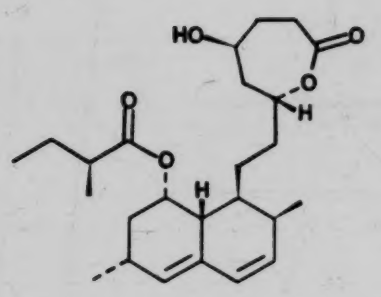
6 R=OH
7 R=H



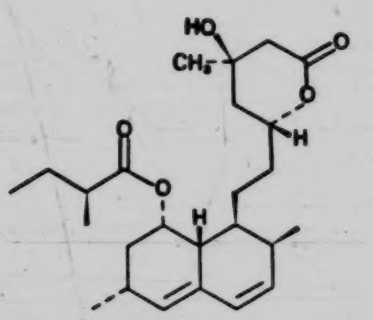
8 R=H
9 R=CH_3

Fermentation has also been used to modify the natural products. For example, ML-236A (**6**) may be produced by fermentation from Compactin,[29] and Compactin is produced from ML-236A (**6**) or ML-236C (**7**) by some Penicillium strains.[30] Microbial oxidation of Mevinolin or Compactin has also served to prepare 3- or 6-hydroxy derivatives.[31-33] Tests to determine the inhibitory activity of these compounds against cholesterol synthesis *in vitro* showed that the addition of an hydroxyl group at the 3 position caused a 2 to 3 fold enhancement of activity.[33]

Still other analogues are available by chemical modification of the natural products. A number of compounds have been prepared where the α-methylbutyrate side chain is replaced by various esters, or ethers.[34-40] Modifications that have been made to the lactone portion include ring expansion to compound **10**, and conversion to the mevalonolactone derivative **11**.[40]



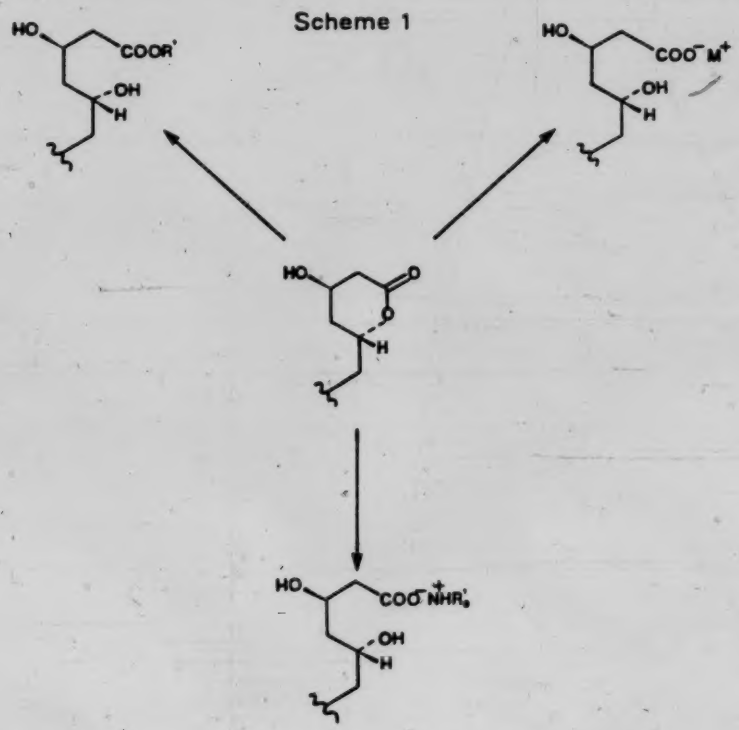
10



11

Opening of the lactone to a dihydroxy acid has permitted preparation of many metal or amine salts of the natural products[41-46] as well as a variety of dihydroxy acid esters[40 43 47] (Scheme 1).

Scheme 1



A number of modifications to the hexahydronaphthalene portion have also been made. These include complete, or partial, reduction of the diene system,[28 37 43 48] cyclopropanation of one or both double bonds,[43] and allylic oxidation.[49]

While such microbial and chemical alterations to the natural products do provide analogues, a much more general approach would be that based on total synthesis. Work in this area is challenging because, in addition to the fact that Mevinolin and Compactin possess 8 and 7 asymmetric centers respectively, they are also highly functionalized and bear a sensitive β-hydroxy-δ-lactone moiety.

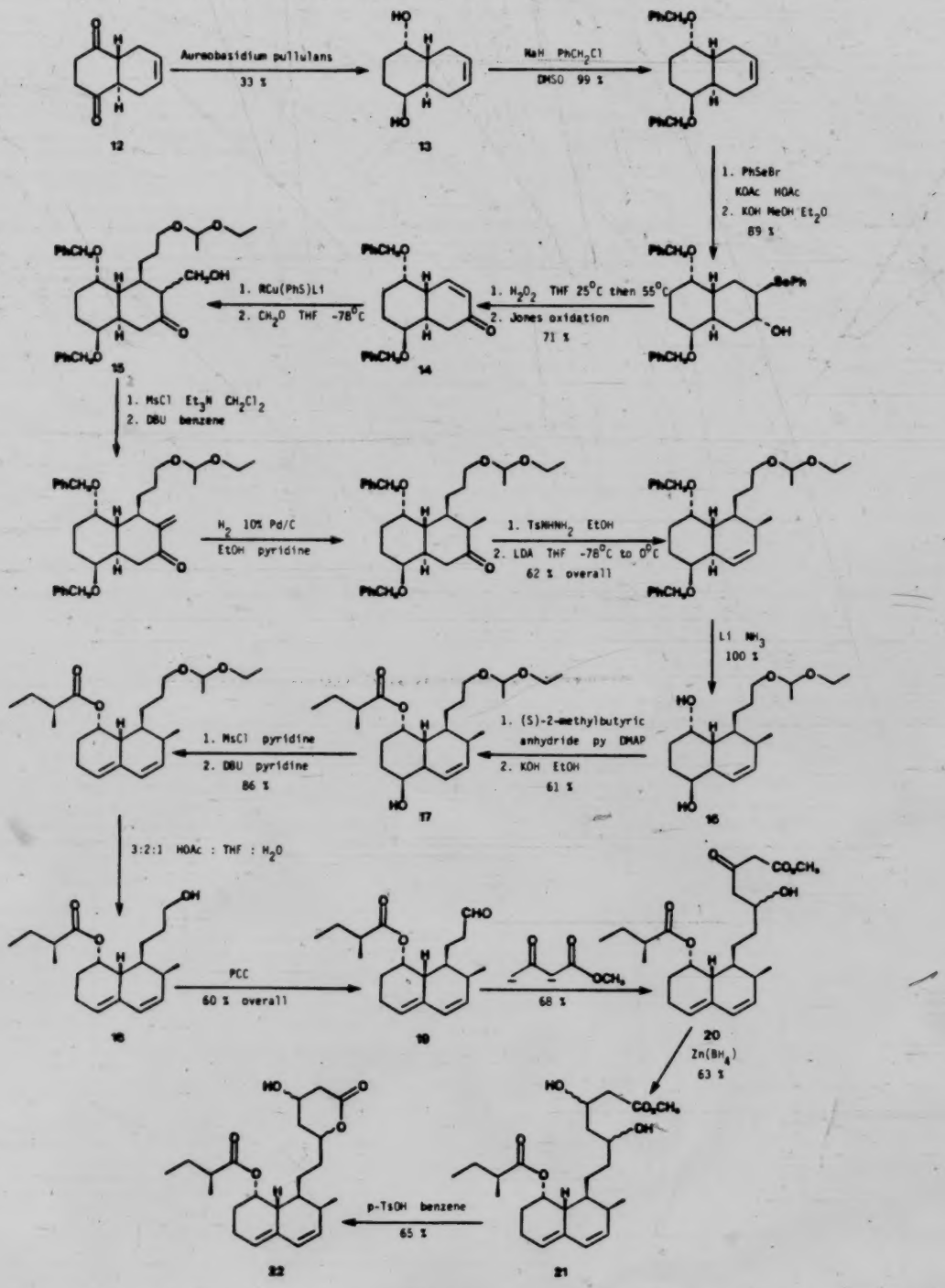
When we began this project late in 1981, no work related to total synthesis of these molecules had appeared in the literature. The perceived importance of the compounds is such, however, that within two years, five syntheses of Compactin[50-55] and one of Mevinolin[56] have been described. In addition, three preparations of the hexahydronaphthalene portion of Compactin,[57-59] one of the corresponding unit of Mevinolin[60] and four synthons for the lactone portion have also appeared.[61-65]

A. Total Syntheses of Mevinolin and Compactin

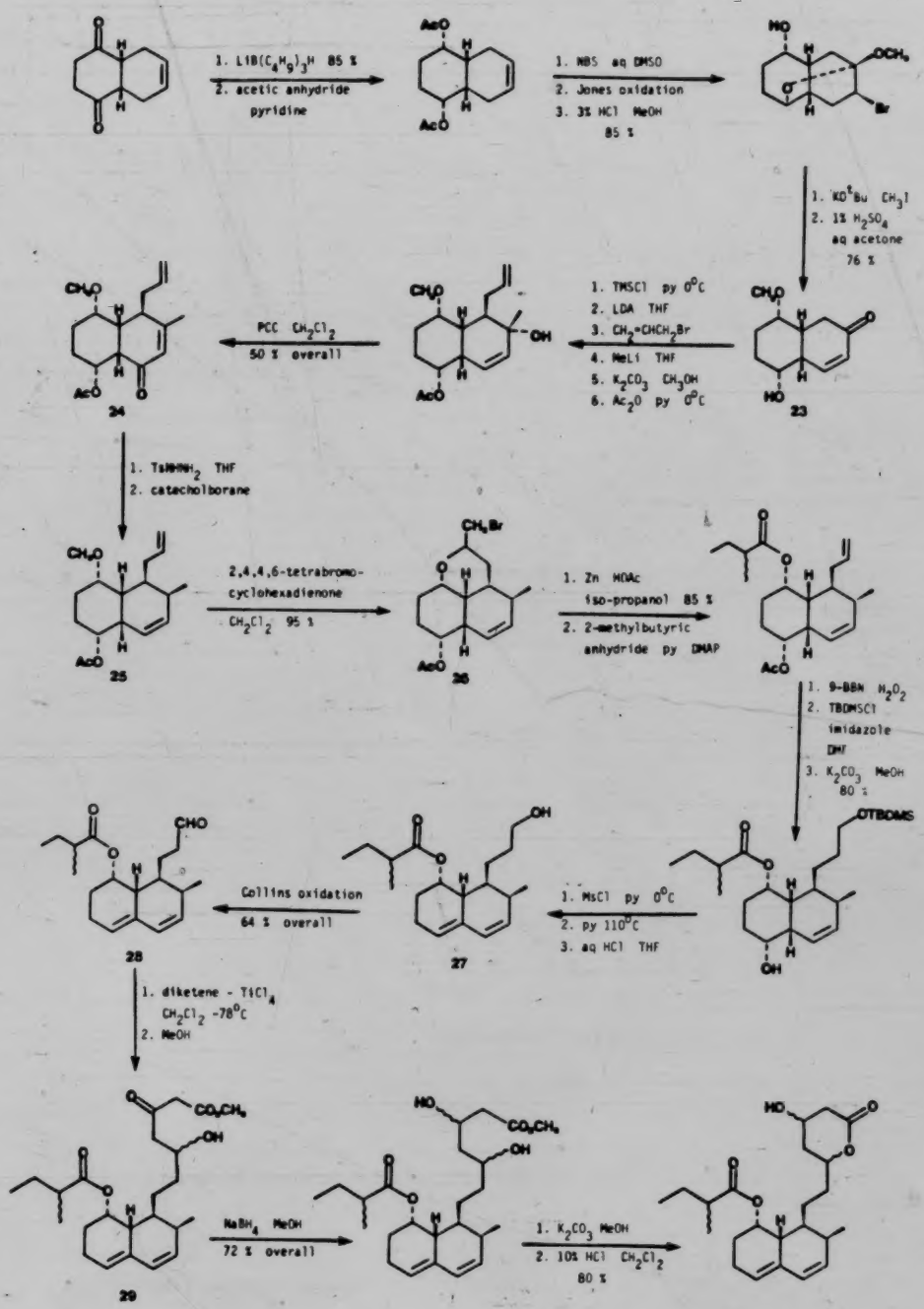
The first reported synthesis of (+)-Compactin is shown in Scheme 2.[50,51] The key chiral intermediate, enone **14**, was prepared in 70% overall yield from optically active ene diol **13** which, in turn, was obtained by microbial reduction of **12**. Cuprate addition to the enone system of **14** occurred exclusively from the convex β-face of the molecule to give the correct C-8 stereochemistry. The resulting enolate was trapped with formaldehyde to produce **15**. Dehydration and hydrogenation generated the C-7 methyl group with the requisite stereochemistry. Elaboration of the hexahydronaphthalene was straightforward, except that it was not possible to selectively esterify the C-1 hydroxyl of **16** so that diesterification, followed by selective hydrolysis of the C-4 butyrate, was used, to make **17**. The lactone portion was added to the bicyclic nucleus by reacting **19** with the dianion of methyl acetoacetate. The resulting inseparable mixture of diastereoisomers **20** was reduced to a mixture of four diastereomeric diols **21**. These were separated into two pairs. One of them was subjected to lactonization to give **22**, as a mixture of two diastereoisomers, from which (+)-Compactin was isolated by HPLC. This route provided optically active Compactin in 14 steps from **14** in 0.8% overall yield.

Another synthesis of (+)-Compactin and also of (±)-Compactin, starts with the *cis*-isomer of enedione **12** and is shown in Scheme 3.[54] In this work the C-7 and C-8 substituents are appended in a somewhat different manner. Allylation of enone **23** after

Scheme 2


Aureobasidium pullulans
33 %
NaH PhCH2Cl
DMSO 99 %
1. PhSeBr
KOAc HOAc
2. KOH MeOH Et2O
89 %
1. H2O2 THF 25°C then 55°C
2. Jones oxidation
71 %
1. RCu(PhS)Li1
2. CH2O THF -78°C
1. MsCl Et3N CH2Cl2
2. DBU benzene
H2 10% Pd/C
EtOH pyridine
1. TsNHNH2 EtOH
2. LDA THF -78°C to 0°C
62 % overall
Li NH3
100 %
1. (S)-2-methylbutyric
anhydride py DMAP
2. KOH EtOH
61 %
1. MsCl pyridine
2. DBU pyridine
86 %
3:2:1 HOAc : THF : H2O
PCC
60 % overall
68 %
Zn(BH4)
63 %
p-TsOH benzene
65 %
12
13
14
15
16
17
18
19
20
21
22

Scheme 3


1. LiB(C4H9)3H 85 %
2. acetic anhydride
pyridine
1. NBS aq DMSO
2. Jones oxidation
3. 3% HCl MeOH
85 %
1. KO^{t}Bu CH3I
2. 1% H2SO4
aq acetone
76 %
1. TMSCl py 0°C
2. LDA THF
3. CH2=CHCH2Br
4. MeLi THF
5. K2CO3 CH3OH
6. Ac2O py 0°C
PCC CH2Cl2
50 % overall
24
23
1. TsNHNH2 THF
2. catecholborane
2,4,4,6-tetrabromo-
cyclohexadienone
CH2Cl2 95 %
25
26
1. Zn HOAc
iso-propanol 85 %
2. 2-methylbutyric
anhydride py DMAP
1. 9-BBN H2O2
2. TBDMSCl
imidazole
DMF
3. K2CO3 MeOH
80 %
1. MsCl py 0°C
2. py 110°C
3. aq HCl THF
Collins oxidation
64 % overall
27
28
1. diketene - TiCl4
CH2Cl2 -78°C
2. MeOH
NaBH4 MeOH
72 % overall
1. K2CO3 MeOH
2. 10% HCl CH2Cl2
80 %
29

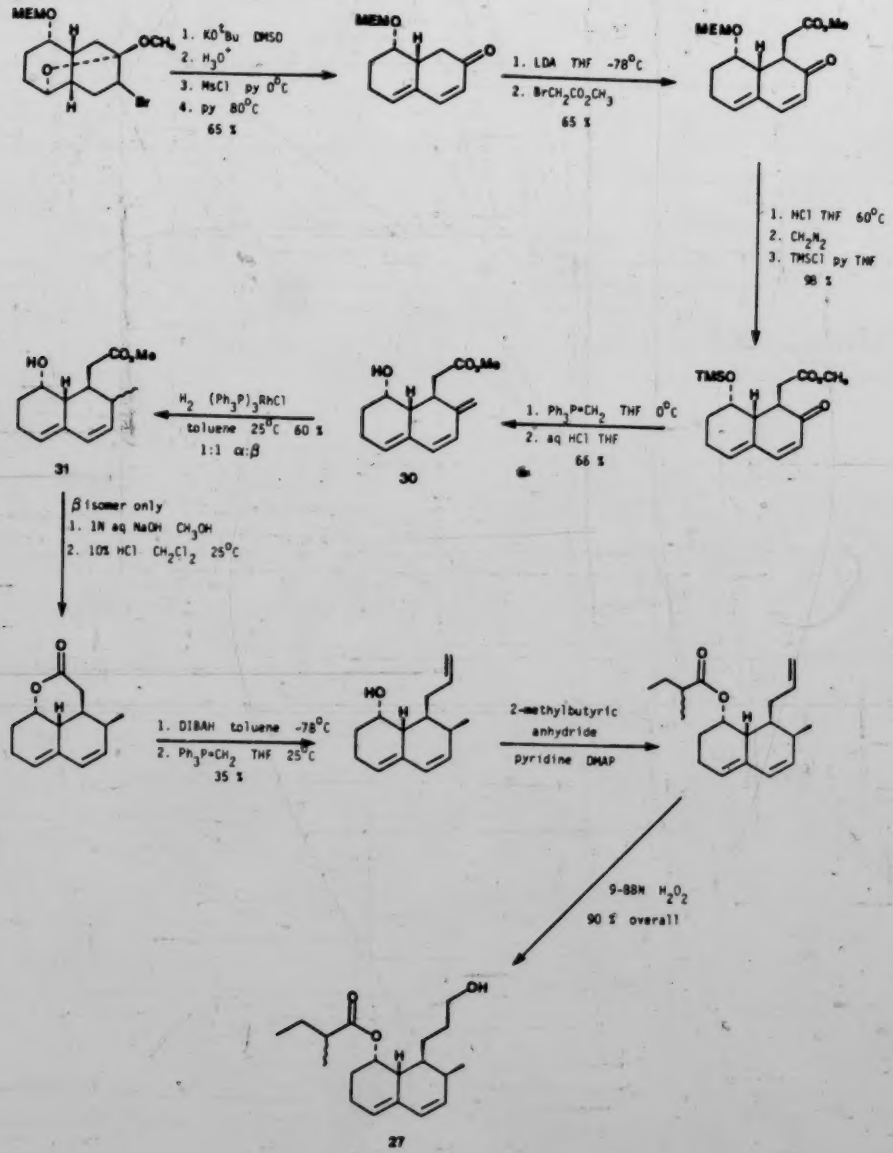
protection of the hydroxyl occurred selectively from the convex β-face of the molecule to establish the proper C-8 stereochemistry. The C-7 methyl group was introduced by treatment of the ketone with methyllithium. The correct C-7 β-stereochemistry and the C-5, C-6 double bond were introduced by catecholborane reduction of the tosylhydrazone derived from enone **24**. Cleavage of the methyl ether in **25** could not be accomplished directly, but rather gave bromoether **26**, which then had to be reduced. Introduction of the lactone portion involved treatment of aldehyde **28** with diketene-$TiCl_4$ followed by methanol to give a mixture of diastereomeric alcohols **29**. The synthesis of (±)-Compactin was completed by the same sequence as in the previously described route to (+)-Compactin.[50,51]

An intermediate, corresponding to **27**, was also prepared using (S)-2-methylbutyric anhydride rather than the racemic reagent. A separable mixture of diastereoisomers was obtained, one of which corresponded to intermediate **18** in the previously described synthesis of (+)-Compactin.[50,51] This sequence therefore constitutes a formal total synthesis of (+)-Compactin.

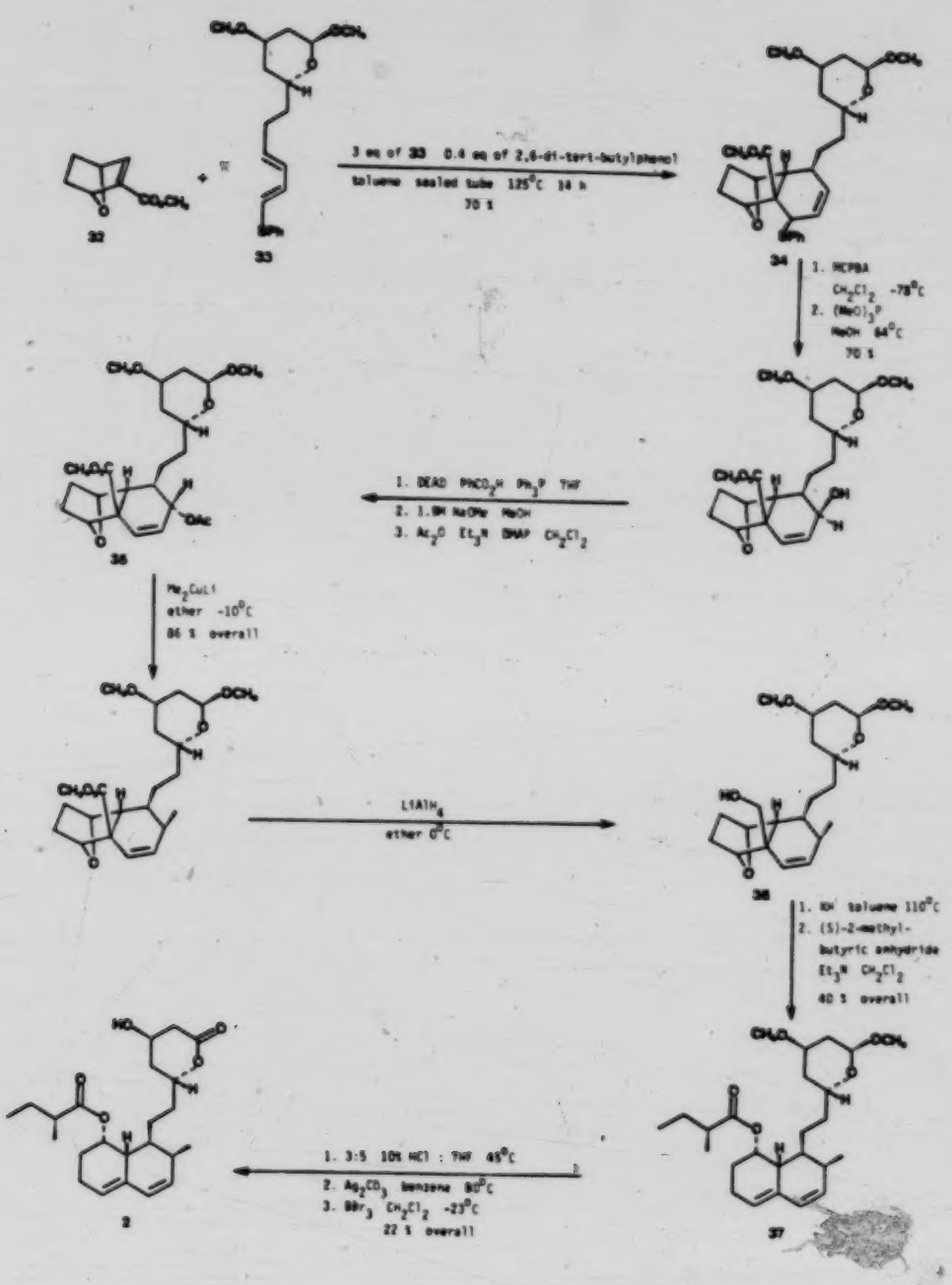
The authors of this work have recently described an alternate, and more efficient, route to compound **27**.[55] In their new approach (Scheme 4), the diene chromophore was generated by regioselective hydrogenation of triene **30**. The resulting diene **31** was a mixture of isomers differing in the stereochemistry of the C-7 methyl group. The correct, β-isomer was converted by a straightforward sequence to compound **27**.

The Diels-Alder reaction has found extensive use in approaches to Mevinolin and Compactin. (+)-Compactin was prepared by the intermolecular Diels-Alder reaction of chiral dienophile **32** with the chiral diene **33** to give, in a single operation, the intact carbon skeleton of (+)-Compactin (Scheme 5).[53] The reaction proceeds by the *endo* addition of **33** to the *exo* face of **32** to form adduct **34** in 70% yield. Introduction of the C-7 methyl group was accomplished by lithium dimethyl cuprate coupling with acetate **35**, itself derived from **34** by sulfoxide-sulfenate rearrangement and Mitsunobu reaction (to adjust the C-7 stereochemistry). The C-4, C-4a double bond and the C-1 α-hydroxyl were established by Grob fragmentation of alcohol **36** to **37**, which was readily converted to (+)-Compactin.

Scheme 4


MEMO
1. KO^{t}Bu DMSO
2. H_3O^+
3. MsCl py 0°C
4. py 80°C
65 %
1. LDA THF -78°C
2. $BrCH_2CO_2CH_3$
65 %
1. HCl THF 60°C
2. CH_2N_2
3. TMSCl py THF
98 %
1. $Ph_3P{=}CH_2$ THF 0°C
2. aq HCl THF
66 %
H_2 $(Ph_3P)_3RhCl$
toluene 25°C 60 %
1:1 α:β
31
30
β isomer only
1. 1N aq NaOH CH_3OH
2. 10% HCl CH_2Cl_2 25°C
1. DIBAH toluene -78°C
2. $Ph_3P{=}CH_2$ THF 25°C
35 %
2-methylbutyric anhydride
pyridine DMAP
9-BBN H_2O_2
90 % overall
27

Scheme 5


3 eq of 33 0.4 eq of 2,6-di-tert-butylphenol
toluene sealed tube 125°C 14 h
70 %
1. MCPBA
CH2Cl2 -78°C
2. (MeO)3P
MeOH 64°C
70 %
1. DEAD PhCO2H Ph3P THF
2. 1.5N NaOMe MeOH
3. Ac2O Et3N DMAP CH2Cl2
Me2CuLi
ether -10°C
86 % overall
LiAlH4
ether 0°C
1. KH toluene 110°C
2. (S)-2-methyl-
butyric anhydride
Et3N CH2Cl2
40 % overall
1. 3:5 10% HCl : THF 45°C
2. Ag2CO3 benzene 80°C
3. BBr3 CH2Cl2 -23°C
22 % overall

Chiral dienophile **32** was prepared (Scheme 6) by a route in which resolution of acid **38** is the key step, whereas diene **33** was prepared in optically active form using the carbohydrate derivative **39** as a source of the chiral centers (Scheme 7).

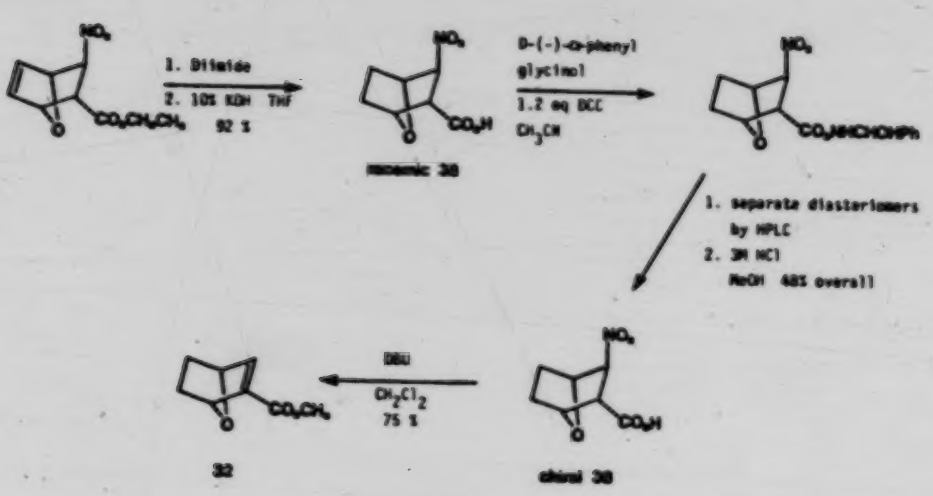
A highly convergent and enantioselective synthesis of (+)-Compactin was achieved based on intramolecular Diels-Alder chemistry (Scheme 8).[52] (*E,E,E*)-Trienone **42** was efficiently prepared by Wadsworth-Emmons coupling of chiral segments **40** and **41**. Cyclization of **42** in refluxing chlorobenzene afforded the desired *trans*-octalone **43** (28%), together with two *cis*-isomers (45% and 9%). K-Selectride reduction of the ketone produced the requisite C-1 α-alcohol. Esterification with (S)-2-methylbutyric anhydride then gave **44**, a compound which embodies all of the chiral centers present in (+)-Compactin. Elaboration of the lactone portion and introduction of the C-4, C-4a double bond completed the synthesis.

Optically active phosphonate **40** was made (Scheme 9) from readily available (4S)-γ-lactone **45**. Stereoselective preparation of the (*E, E*)-diene **47** was accomplished by addition of *trans*-crotyl phenyl sulfone anion to aldehyde **46** followed by quenching with acetic anhydride and reductive removal of the sulfone and acetate units.

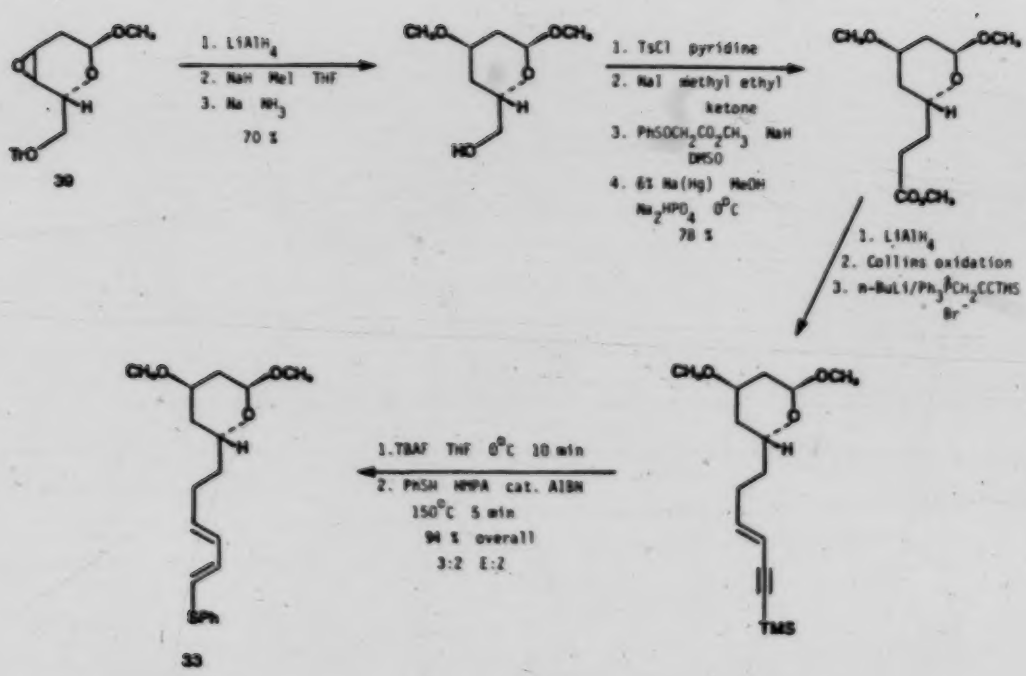
The synthesis of **41** (Scheme 10) depended on the asymmetric reduction of β-keto acid derivatives by Baker's yeast.

The versatility of this Compactin synthesis was demonstrated by conversion of compound **43** into Mevinolin (Scheme 11).[56] This scheme represents the first and, to date, only total synthesis of Mevinolin. There exists an additional chiral center (C-3) in Mevinolin, compared to Compactin. This center was introduced stereospecifically by Michael addition of lithium dimethyl cuprate to enone **48**, derived from **43** by silyl enol ether formation and oxidation. The cuprate addition proceeded exclusively from the α-face of the molecule because the bulky *tert*-butyldimethylsilyl group hindered attack from the β-face. Ketone **49** was converted into Mevinolin by a route analogous to that used for the synthesis of Compactin.[52]

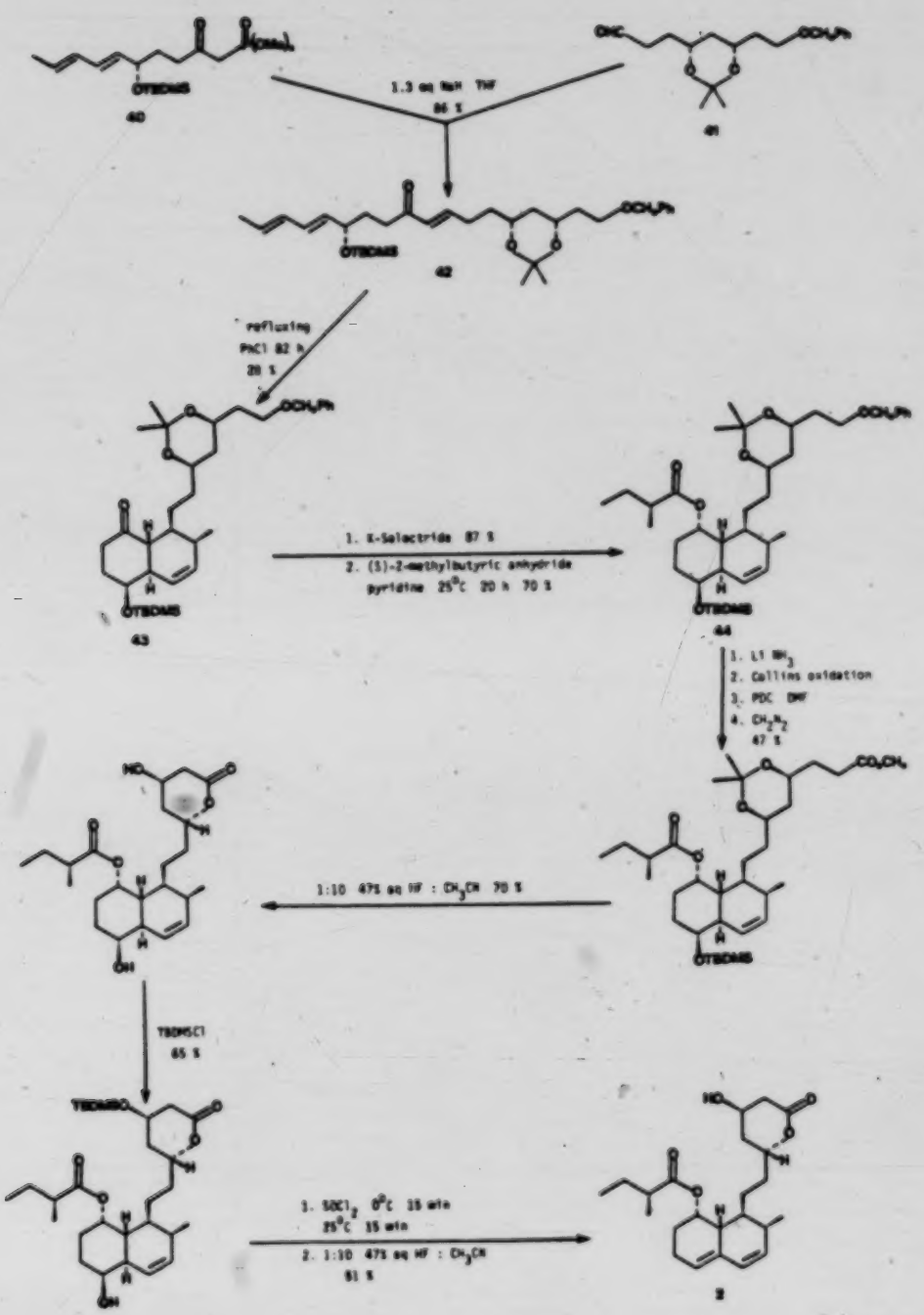
Scheme 6



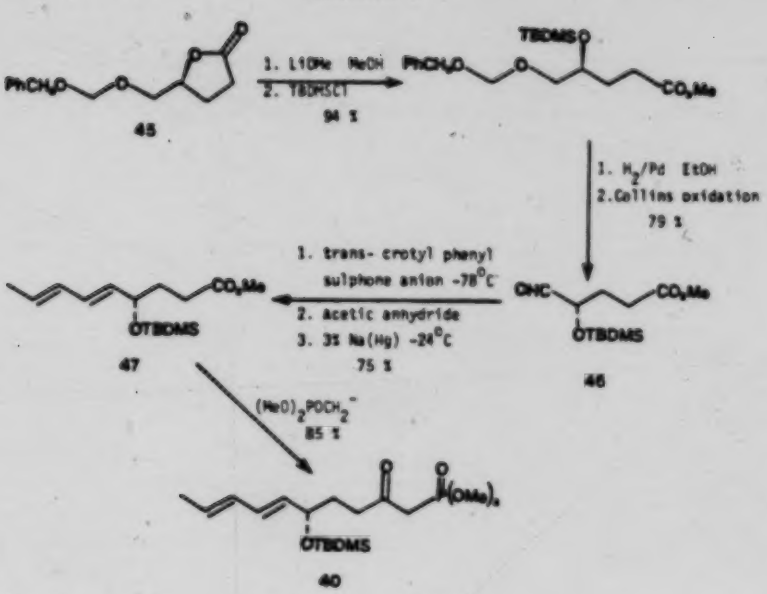
Scheme 7



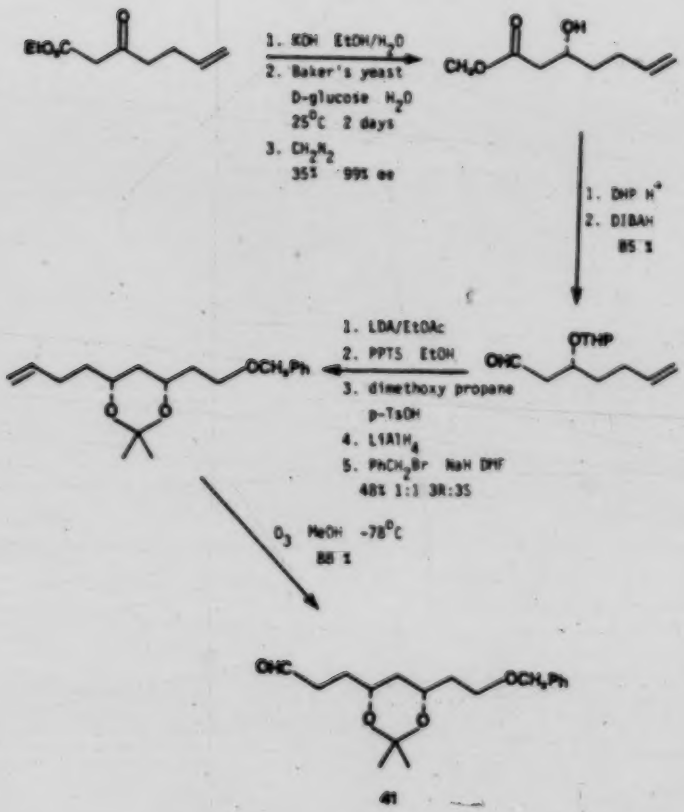
Scheme 8


1.3 eq NaH THF
86 %
40
41
42
refluxing
PhCl 82 h
28 %
1. K-Selectride 87 %
2. (S)-2-methylbutyric anhydride
pyridine 25°C 20 h 70 %
43
44
1. LiBH4
2. Collins oxidation
3. PDC DMF
4. CH2N2
47 %
1:10 47% aq HF : CH3CN 70 %
TBDMSCl
65 %
1. SOCl2 0°C 15 min
25°C 15 min
2. 1:10 47% aq HF : CH3CN
61 %
2

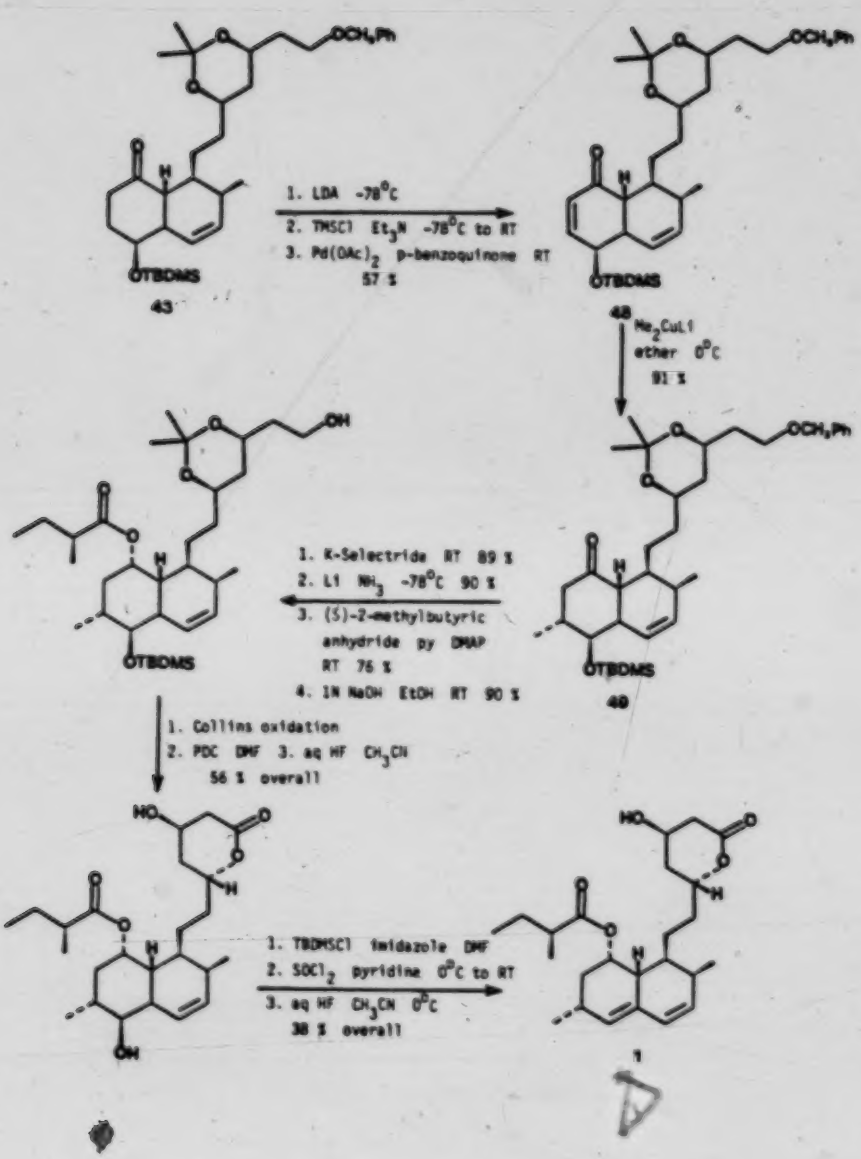
Scheme 9



Scheme 10



Scheme 11


OCH2Ph
OTBDMS
43
1. LDA -78°C
2. TMSCl Et3N -78°C to RT
3. Pd(OAc)2 p-benzoquinone RT
57 %
48
Me2CuLi
ether 0°C
91 %
OH
1. K-Selectride RT 89 %
2. Li NH3 -78°C 90 %
3. (S)-2-methylbutyric anhydride py DMAP RT 76 %
4. 1N NaOH EtOH RT 90 %
49
1. Collins oxidation
2. PDC DMF 3. aq HF CH3CN
56 % overall
HO
1. TBDMSCl imidazole DMF
2. SOCl2 pyridine 0°C to RT
3. aq HF CH3CN 0°C
38 % overall
1

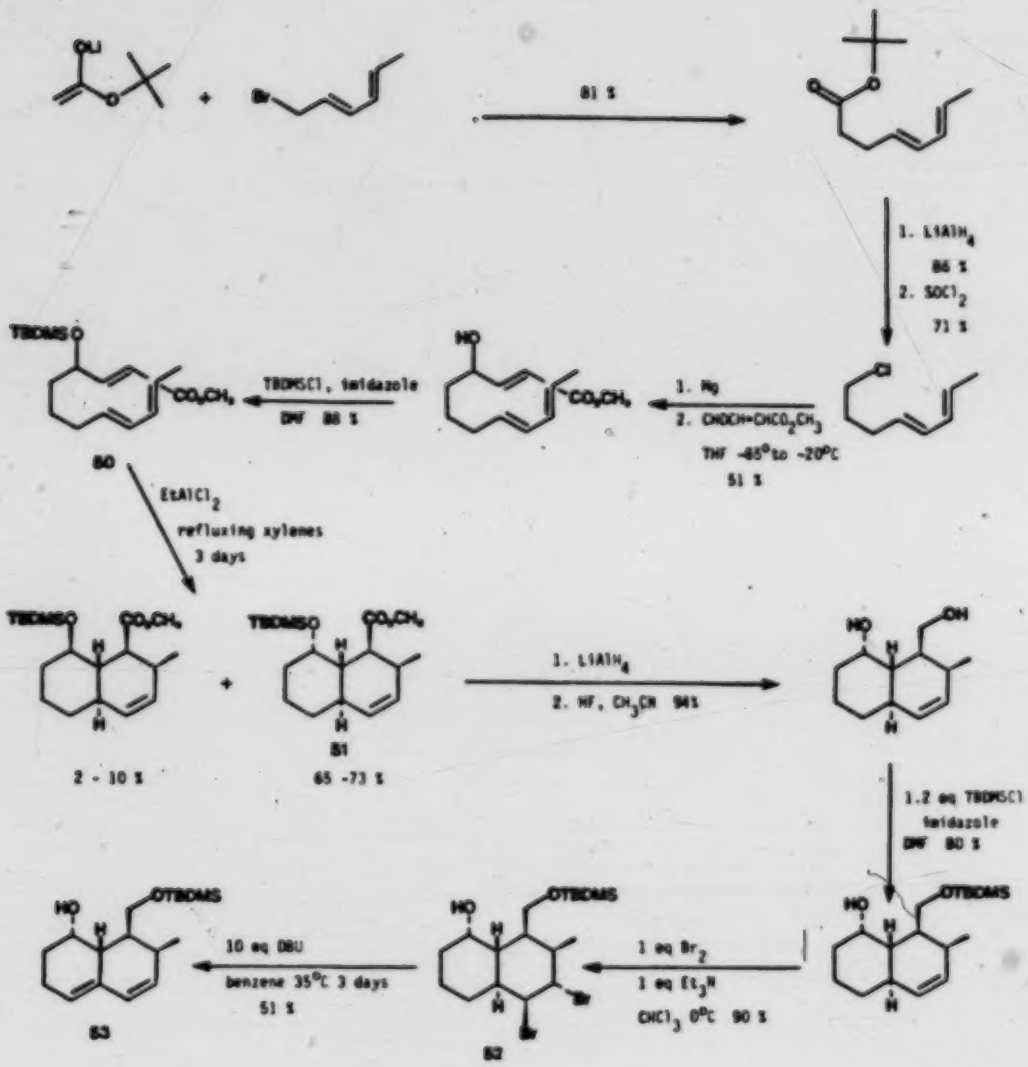
B. Syntheses of the Hexahydronaphthalene Portion of Mevinolin and Compactin

The intramolecular Diels-Alder reaction has also been employed in a number of syntheses of the hexahydronaphthalene portion of Mevinolin and Compactin. In one such approach (Scheme 12), *trans*-octalone **51** was prepared efficiently by the Lewis acid mediated intramolecular Diels-Alder reaction of triene **50**.[57] Bromination, and double dehydrobromination of **52** afforded diene **53**, a compound which represents the hexahydronaphthalene segment of Compactin.

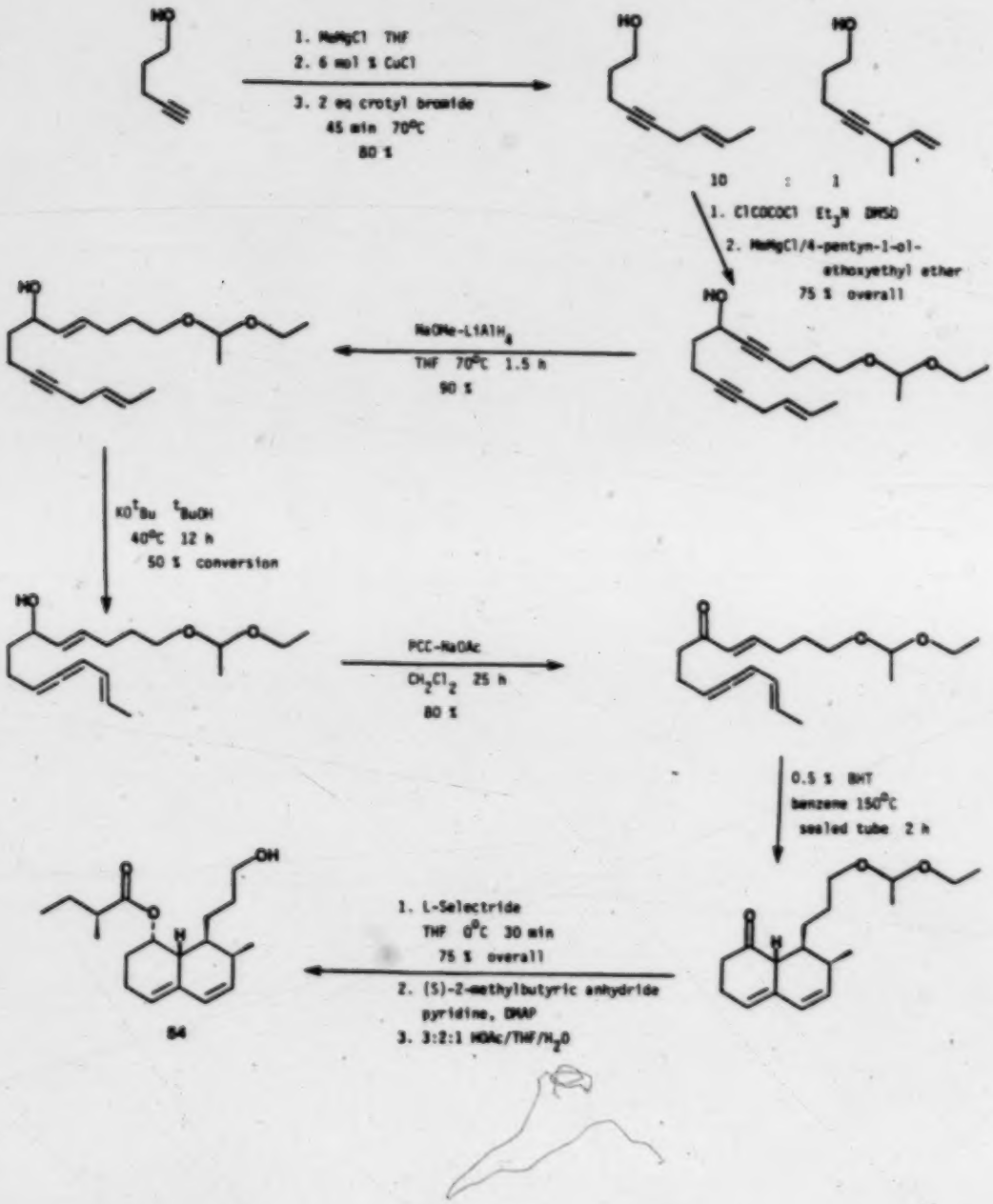
Both double bonds of the diene can be introduced during the intramolecular Diels-Alder step if a vinylallene serves as the diene component. This is demonstrated in Schemes 13 and 14 for the preparation of the hexahydronaphthalenes corresponding to Compactin[51] and Mevinolin[60] respectively. The vinylallene was synthesized by isomerization of a readily available 1,4-enyne. Compound **54** in Scheme 13 is a separable mixture of two diastereoisomers, one of which corresponds to intermediate **18** which had previously been converted to (+)-Compactin,[50,51] and so this scheme represents a formal total synthesis of (+)-Compactin.

A conceptually different approach to the hexahydronaphthalene portion of Compactin is given in Scheme 15.[59] Here, the bicyclic unit is constructed by annellating the left hand ring onto the right hand one. The *cis*-relationship between the C-7 and C-8 substituents was established by the Diels-Alder addition of ethyl (*Z*)-crotonate (**55**) to Danishefsky's diene (**56**), to give adduct **57**, which was elaborated to enone **58**. Attachment of the left hand ring was accomplished by conjugate addition of lithiated dithiane **59** followed by aldol condensation. Hydrolysis of dithiane **61** and L-Selectride reduction of the derived ketone established stereoselectively the C-1 α-hydroxyl group. Esterification with (S)-2-methylbutyric anhydride gave **62** as a mixture of two diastereoisomers. This compound represents the lower part of Compactin. Compound **60** was also converted by a slightly different series of reactions (Scheme 16) into compound **63**, an analogue of **62** in which the diene system occupies the 3, 4, 4a, 5 positions.

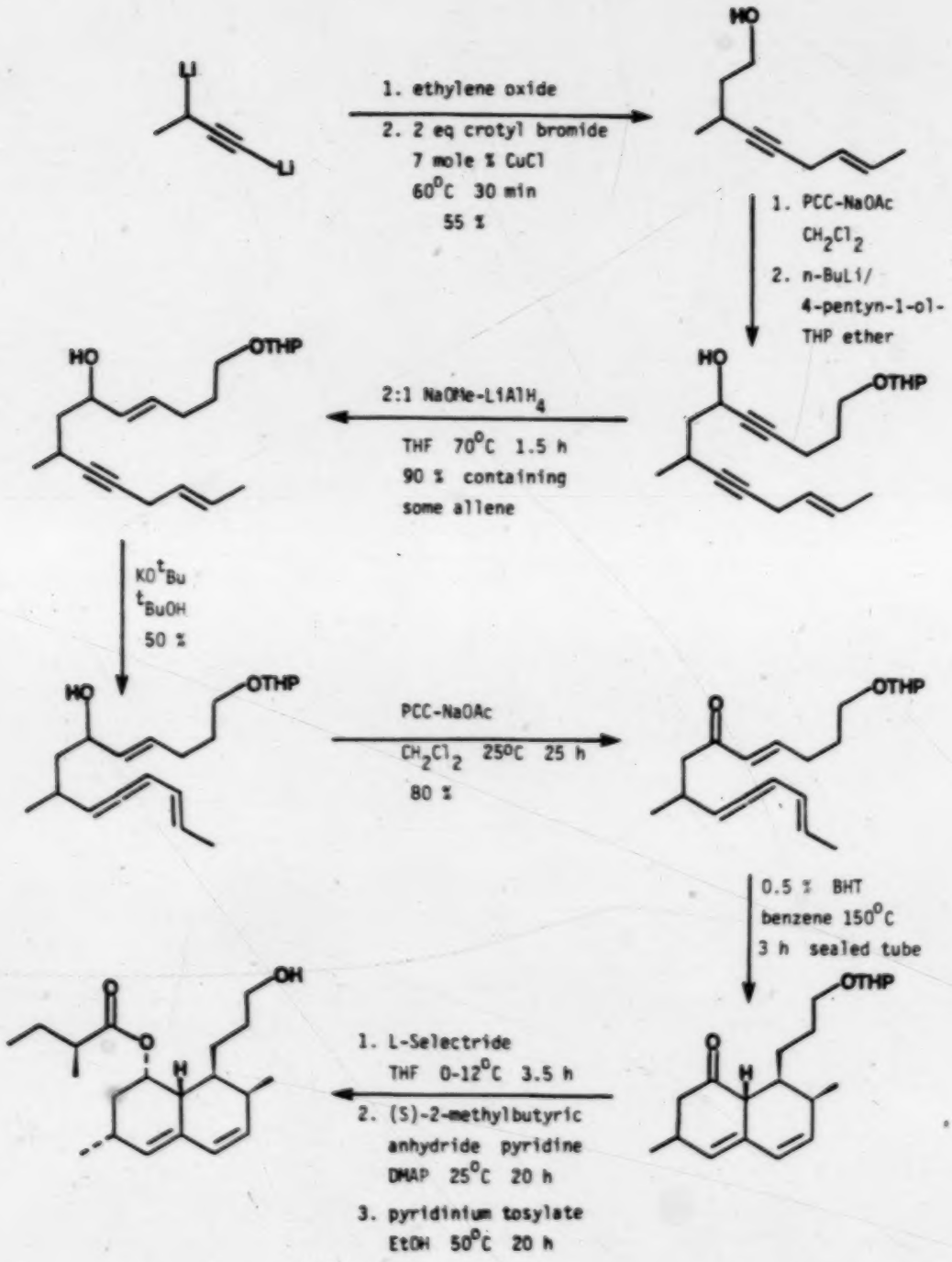
Scheme 12


81 %
1. LiAlH4
86 %
2. SOCl2
71 %
1. Mg
2. CHOCH=CHCO2CH3
THF -65°to -20°C
51 %
TBDMSCl, imidazole
DMF 88 %
80
EtAlCl2
refluxing xylenes
3 days
2 - 10 %
81
65 -73 %
1. LiAlH4
2. HF, CH3CN 94%
1.2 eq TBDMSCl
imidazole
DMF 80 %
1 eq Br2
1 eq Et3N
CHCl3 0°C 90 %
82
10 eq DBU
benzene 35°C 3 days
51 %
83

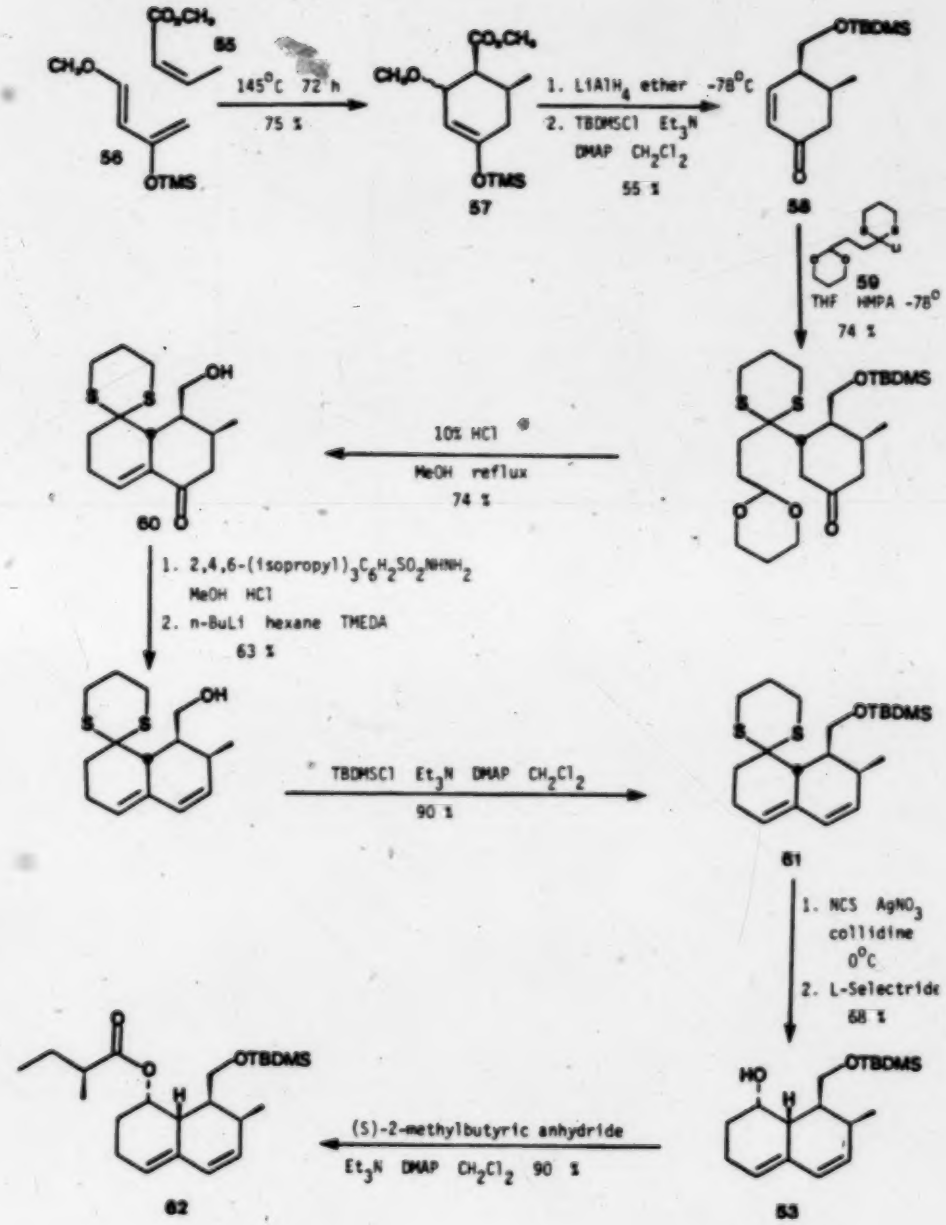
Scheme 13


1. MeMgCl THF
2. 6 mol % CuCl
3. 2 eq crotyl bromide
45 min 70°C
80 %
10 : 1
1. ClCOCOCl Et3N DMSO
2. MeMgCl/4-pentyn-1-ol-ethoxyethyl ether
75 % overall
NaOMe-LiAlH4
THF 70°C 1.5 h
90 %
KO tBu tBuOH
40°C 12 h
50 % conversion
PCC-NaOAc
CH2Cl2 25 h
80 %
0.5 % BHT
benzene 150°C
sealed tube 2 h
1. L-Selectride
THF 0°C 30 min
75 % overall
2. (S)-2-methylbutyric anhydride
pyridine, DMAP
3. 3:2:1 HOAc/THF/H2O
84

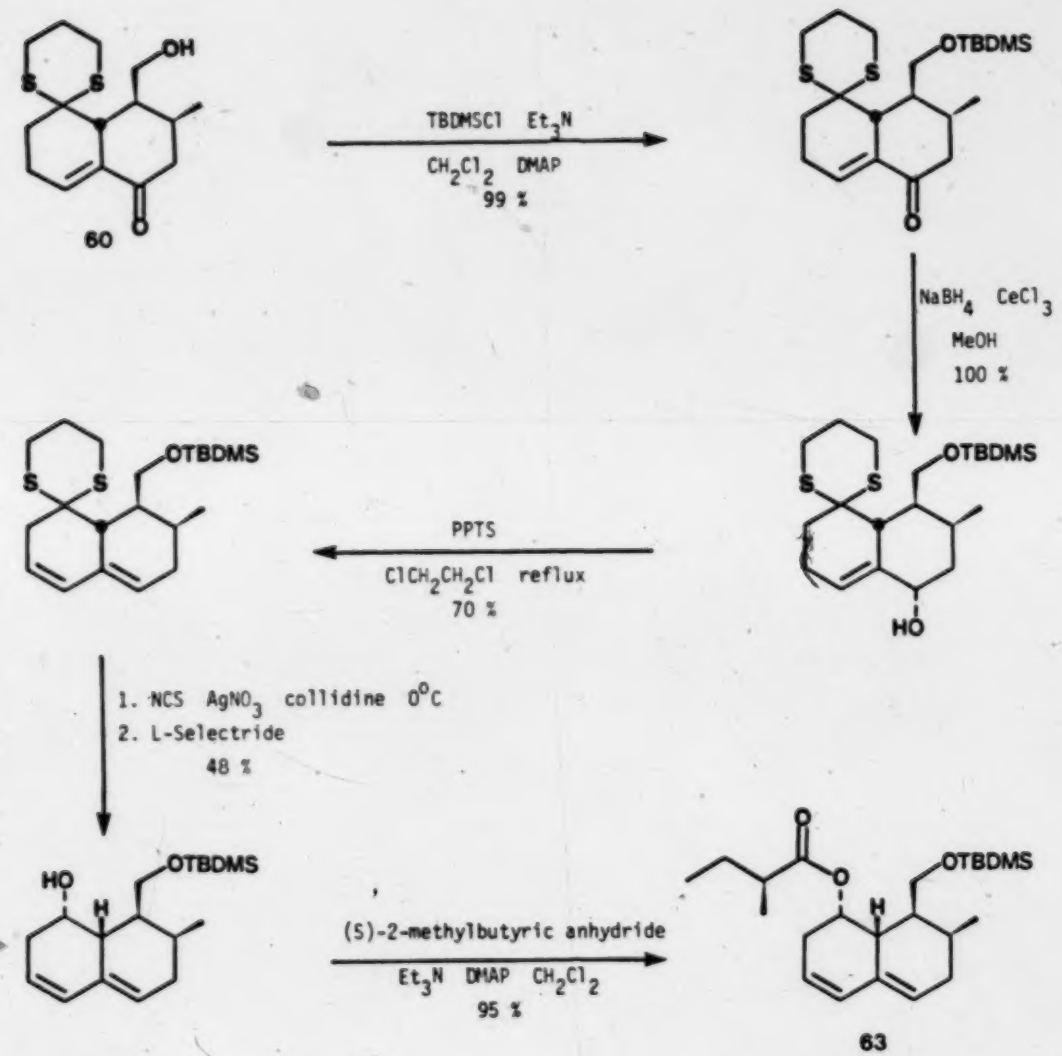
Scheme 14


Li
Li
1. ethylene oxide
2. 2 eq crotyl bromide
7 mole % CuCl
60°C 30 min
55 %
HO
1. PCC-NaOAc
CH2Cl2
2. n-BuLi/
4-pentyn-1-ol-
THP ether
HO
OTHP
2:1 NaOMe-LiAlH4
THF 70°C 1.5 h
90 % containing
some allene
HO
OTHP
KO tBu
tBuOH
50 %
HO
OTHP
PCC-NaOAc
CH2Cl2 25°C 25 h
80 %
OTHP
0.5 % BHT
benzene 150°C
3 h sealed tube
OTHP
H
1. L-Selectride
THF 0-12°C 3.5 h
2. (S)-2-methylbutyric
anhydride pyridine
DMAP 25°C 20 h
3. pyridinium tosylate
EtOH 50°C 20 h
OH
O
O
H

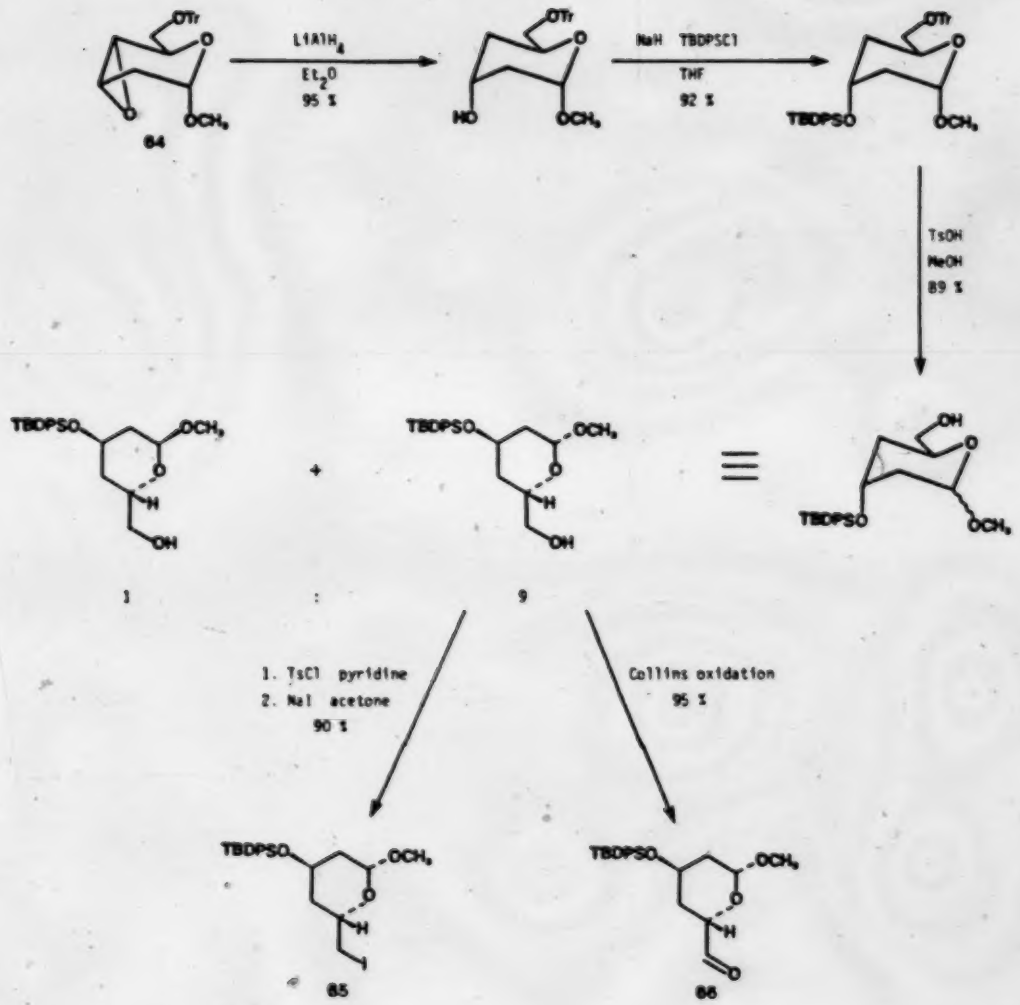
Scheme 15


145°C 72 h
75 %
1. LiAlH4 ether -78°C
2. TBDMSCl Et3N
DMAP CH2Cl2
55 %
59
THF HMPA -78°
74 %
10% HCl
MeOH reflux
74 %
1. 2,4,6-(isopropyl)3C6H2SO2NHNH2
MeOH HCl
2. n-BuLi hexane TMEDA
63 %
TBDMSCl Et3N DMAP CH2Cl2
90 %
1. NCS AgNO3
collidine
0°C
2. L-Selectride
68 %
(S)-2-methylbutyric anhydride
Et3N DMAP CH2Cl2 90 %
55
56
57
58
60
61
62
63
OTBDMS
OTMS
OH
HO

Scheme 16


OH
S
S
O
60
TBDMSCl Et3N
CH2Cl2 DMAP
99 %
OTBDMS
NaBH4 CeCl3
MeOH
100 %
HO
PPTS
ClCH2CH2Cl reflux
70 %
1. NCS AgNO3 collidine 0°C
2. L-Selectride
48 %
H
(S)-2-methylbutyric anhydride
Et3N DMAP CH2Cl2
95 %
63

Scheme 17


OTr
O
OCH3
LiAlH4
Et2O
95 %
HO
NaH TBDPSCl
THF
92 %
TBDPSO
TsOH
MeOH
89 %
OH
1
:
9
1. TsCl pyridine
2. NaI acetone
90 %
Collins oxidation
95 %
I
O
84
85
86

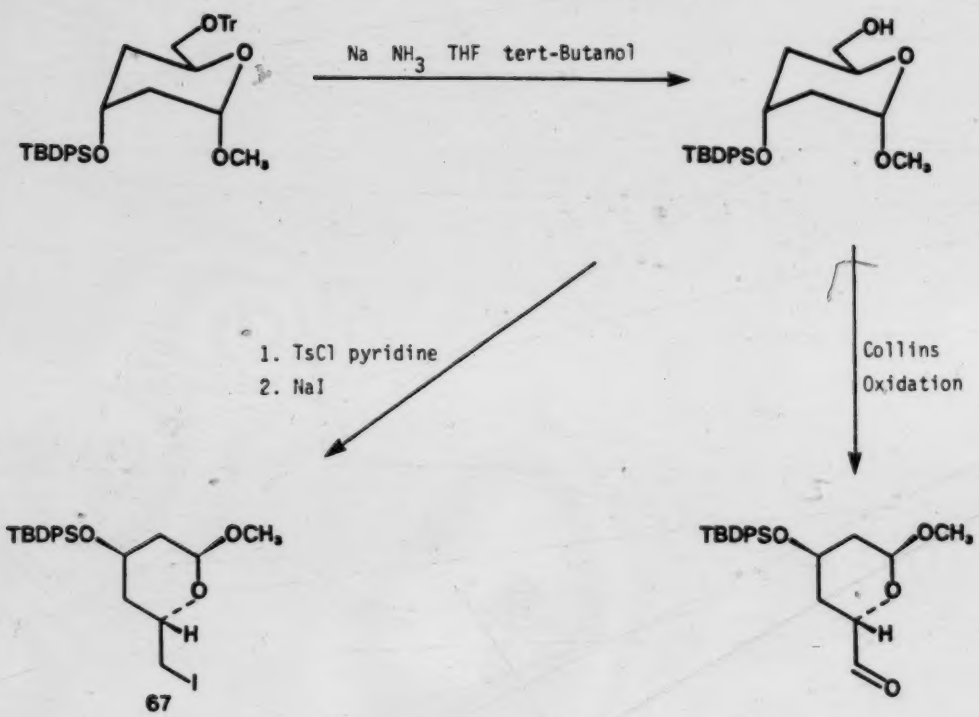
C. Lactone Synthons

A number of synthons for the lactone unit of Mevinolin and Compactin have also been described and in most cases, glucose derivatives were used as appropriate chiral starting materials.

One synthesis, from the known epoxy trityl ether **64**, is shown in Scheme 17 and was used to prepare the two chiral lactone synthons **65** and **66**.[61]

The α-anomers of these synthons were made by an almost identical route (Scheme 18).[62]

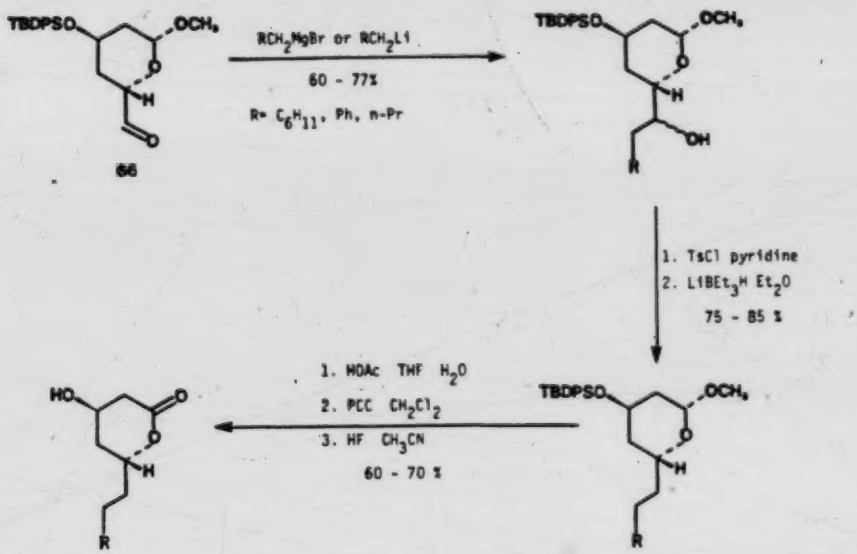
Scheme 18



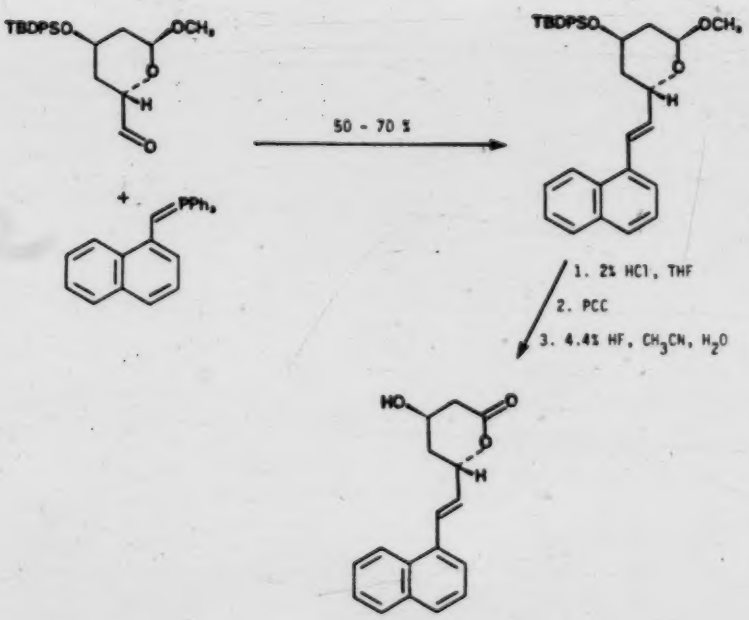
Coupling of these synthons with various lower portions, and elaboration to β-hydroxy-δ-lactones is shown in Schemes 19-21.

A slightly different route starting from methyl α-D-glucopyranoside **68** is summarized in Scheme 22.[63,64] This lactone synthon **69** differs from **67** only in that a benzyl protecting group has replaced the *tert*-butyldiphenylsilyl group.

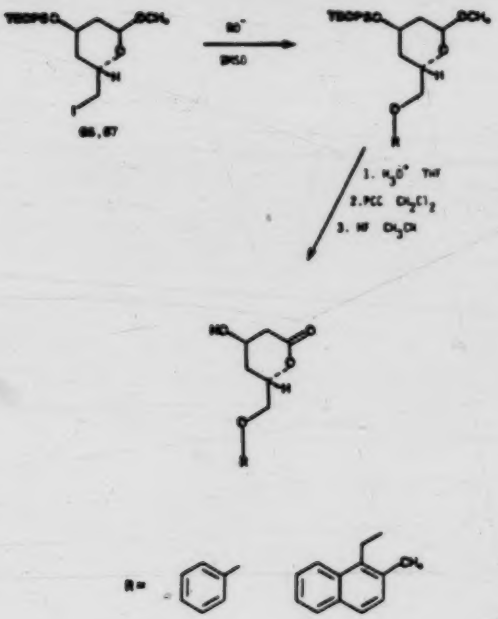
Scheme 19



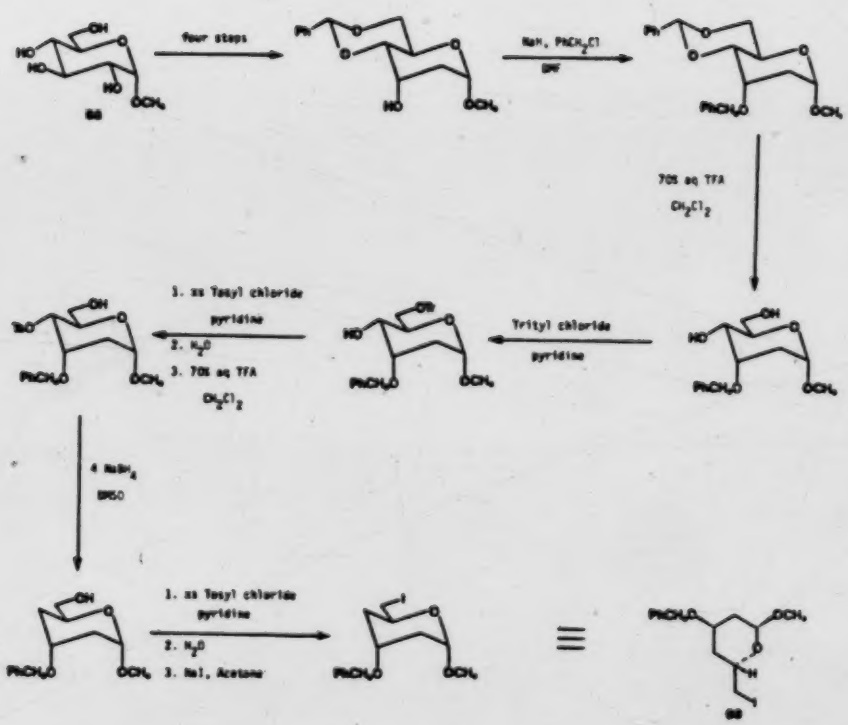
Scheme 20



Scheme 21



Scheme 22



Lactone synthon **69** was used to alkylate the anion of some sulfoxides and sulfones (Scheme 23)[63, 64] and a procedure was developed for elaborating this unit into a β-hydroxy-δ-lactone (Scheme 24).[64]

Another, very different, approach was used to prepare a chiral lactone synthon (Scheme 25).[65] In this procedure the key step involves cyclocondensation of aldehyde **70** with the highly functionalized diene **56**. Thus, aldehyde **70** reacted with Danishefsky's diene **56** under Lewis acid catalysis to form adduct **71** with complete Cram rule selectivity. By using a chiral aldehyde, the requisite absolute stereochemistry was obtained. Addition of isopropanol to the enone system of **71** and reduction with L-Selectride occurred completely stereoselectively. Acetylation of the alcohol and modification of the side chain completed the synthesis of **72**, which possesses both the relative and absolute stereochemistry of the natural products.

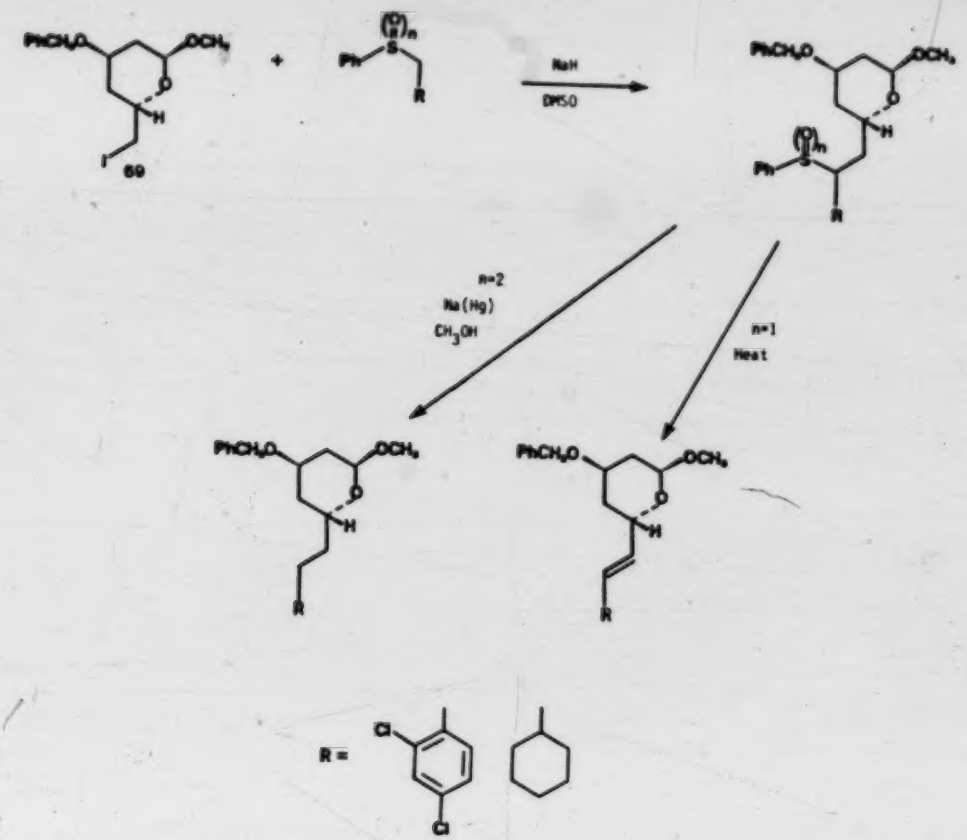
Clearly, a great deal of research has been directed towards the total synthesis of Mevinolin and Compactin, as well as to portions of these molecules. The perceived importance of the compounds and their analogues, both for the purpose of understanding their biological properties and as a challenge to synthetic chemistry will no doubt stimulate further work in this field.

When we considered our approach towards the total synthesis of Mevinolin and Compactin, we sought a highly convergent synthesis, and one that would be flexible enough so that a variety of analogues could be prepared without any substantial modifications to the general plan.

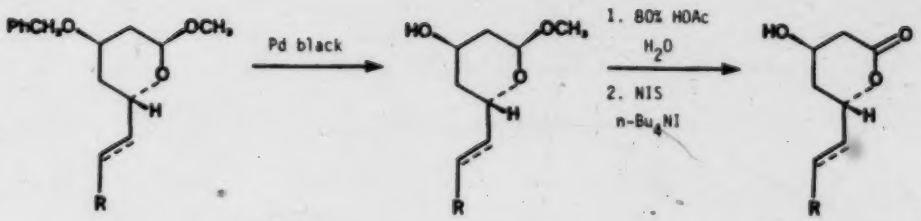
Retrosynthetic analysis suggested that these compounds could be constructed from three parts (shown in Scheme 26 with protecting groups omitted). The α-methylbutyric acid side chain is now commercially available (Aldrich) as its acid chloride and could be appended to the hexahydronaphthalene by a simple reaction.

The lactone synthon contains both of the chiral centers present in the corresponding portion of the natural products and could, in principle, be attached to the bicyclic unit by nucleophilic opening of the epoxide. Oxidative ring closure would complete elaboration of the lactone. Our strategy to efficiently construct the lactone synthon in optically active form was to start with one chiral center intact and to induce the second center of chirality. The preparation of just such a lactone synthon has been

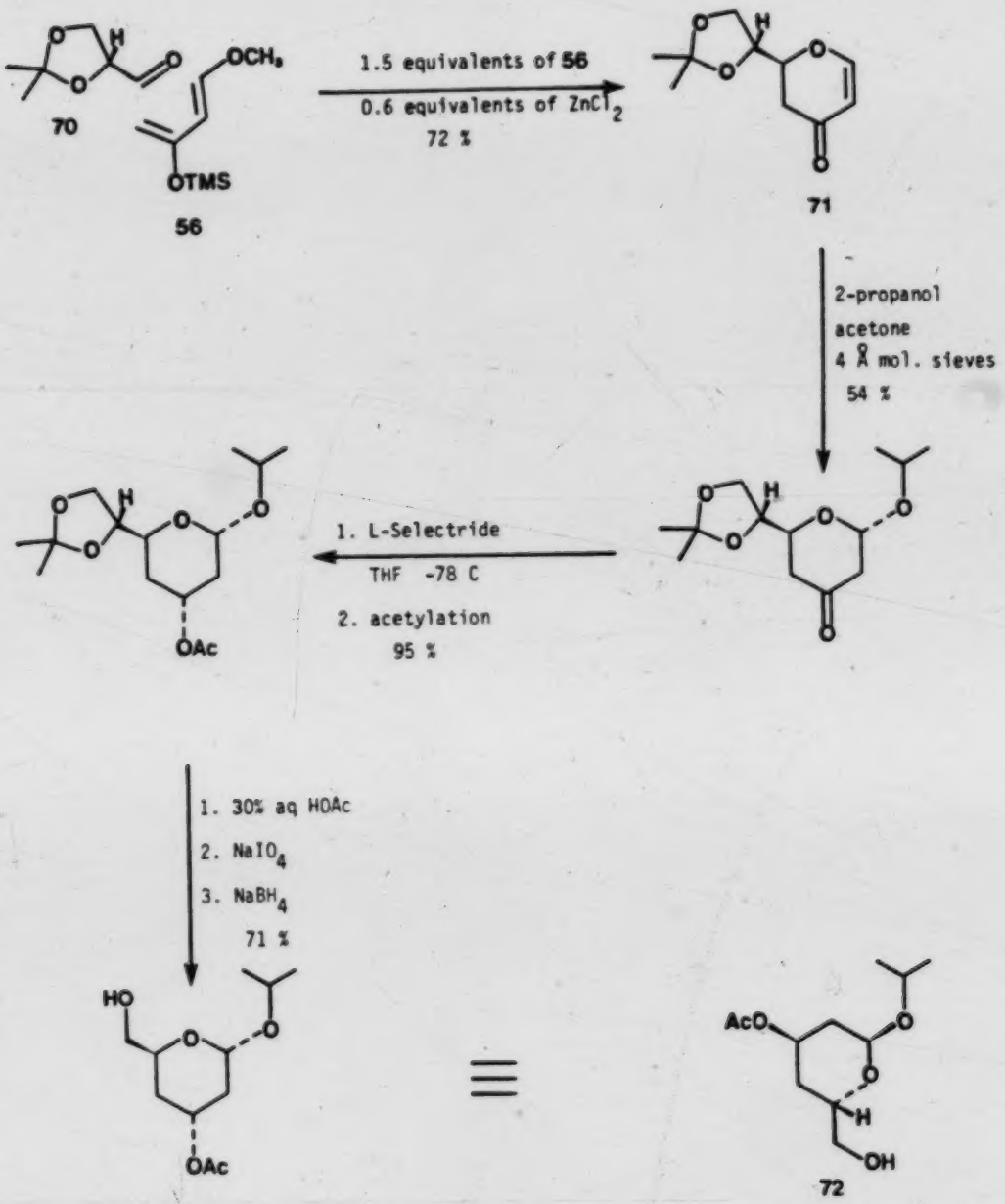
Scheme 23



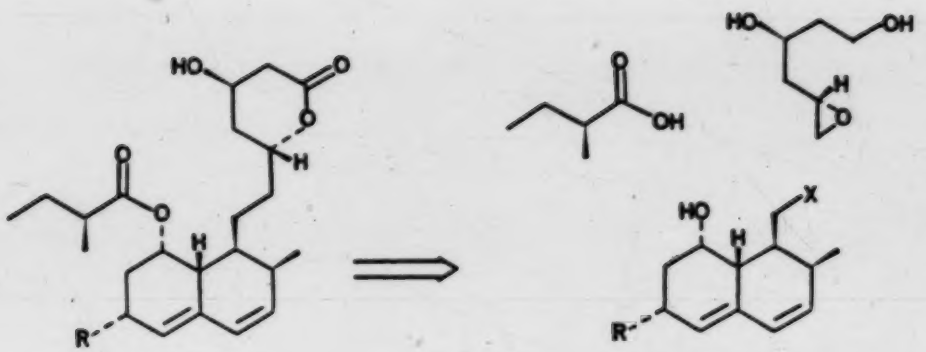
Scheme 24



Scheme 25


70
OCH3
OTMS
56
1.5 equivalents of 56
0.6 equivalents of ZnCl2
72 %
71
2-propanol
acetone
4 Å mol. sieves
54 %
1. L-Selectride
THF -78 C
2. acetylation
95 %
OAc
1. 30% aq HOAc
2. NaIO4
3. NaBH4
71 %
HO
OAc
AcO
OH
72

Scheme 26



completed in our laboratory and is outlined in Scheme 27.[44] The sequence begins with readily available (S)-malic acid **73** and, by a series of straightforward transformations, converts it into the key chiral homoallylic alcohol **75**. The second center of chirality was introduced at this stage by iodocarbonation, to afford compound **76** and its C-5 epimer in a ratio of about 9 to 1. Treatment of compound **76** with base produced epoxy alcohol **77** which was protected as its THP ether so as to provide the required target molecule **78**.

The hexahydronaphthalene portions of Mevinolin and Compactin (Figure 1) contain five and four chiral centers respectively.

Our plan for attachment of these units to the chiral lactone sython **78** involved nucleophilic opening of epoxide **78** by the carbon bearing the substituent X (see Figure 1). For our purposes, an hydroxyl group was chosen as group X because it is easy to replace by a number of anion stabilizing groups. We considered that a convergent approach to the hexahydronaphthalene would involve building up this system by annellating the left hand ring of the bicyclic unit onto a pre-existing right hand ring. Our anellation strategy, outlined in Scheme 28, involved intramolecular carbonyl coupling of an aldehyde enone to form the C-4, C-4a double bond, and an aldol condensation to make the C-1, C-8a single bond. This aldol condensation would be expected to occur from the less hindered face

Scheme 27

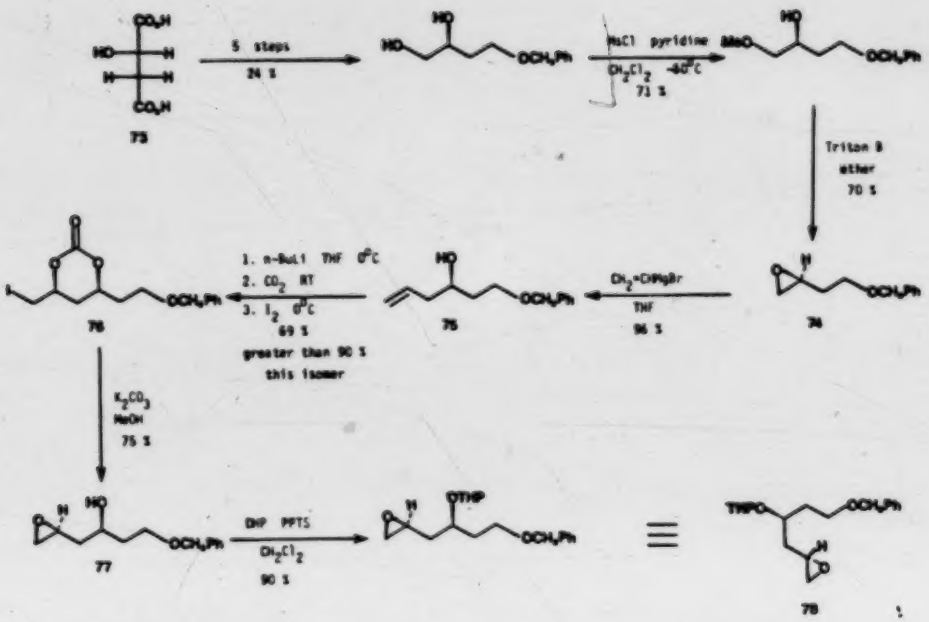
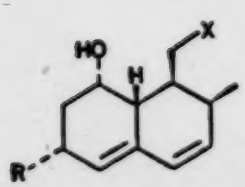


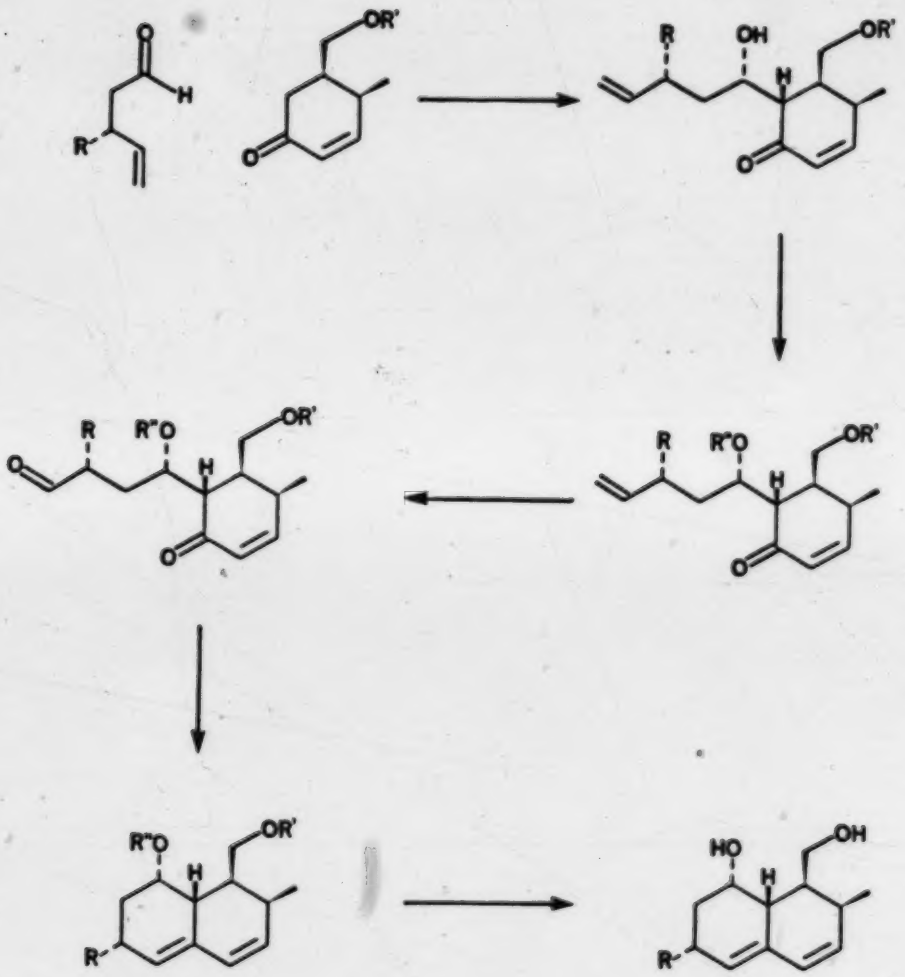
Figure 1



R=CH_3, H

of the enone to generate the desired ring junction stereochemistry at C-8a. The aldehyde functionality required for intramolecular carbonyl coupling would have to be masked during early stages of the work and we felt that a carbon-carbon double bond would serve this purpose well.

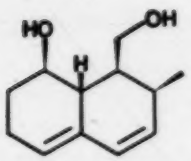
Scheme 28



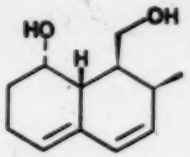
In the following section, four topics will be discussed:

A. Model studies that establish the viability of the anellation plan outlined in Scheme 28.

B. The synthesis of compounds **127b** and **127a** by that route. These are substances which represent the hexahydronaphthalene portion of (±)-Compactin and of its C-1 epimer.

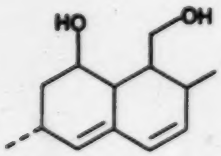


127a



127b

C. The use of the same general approach to prepare compound **138** as a mixture of diastereoisomers, a consequence of using a racemic right hand ring and an optically active precursor to the left hand portion. Compound **138** possesses the appropriate features of the bicyclic system of Mevinolin.



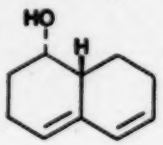
138

D. Preliminary model studies on coupling the hexahydronaphthalene portion to our chiral lactone synthon.

II. RESULTS AND DISCUSSION*

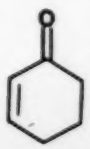
A. Model Studies on the Annellation Approach

In order to determine the viability of our strategy (outlined in Scheme 28) for preparation of the bicyclic unit, we attempted to make the model compound **103b**.

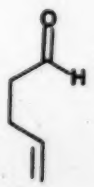


103b

According to our plan, **103b** would be constructed from 2-cyclohexenone (**79**) and 4-pentenal (**80**). The latter is a known compound,[65] and it was prepared by two different procedures.

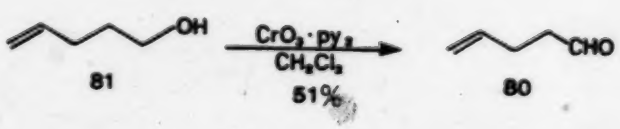


79



80

The most direct route, Collins oxidation[70] of 4-pentenol (**81**), gave only a modest yield (equation 2).



81 51% **80** (2)

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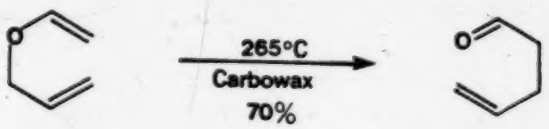
*Some of these results have previously been reported.[67,68]

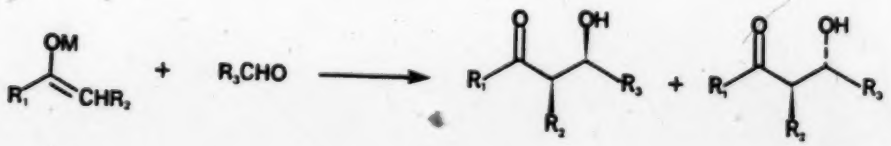
Furthermore, the reaction was inconvenient because rather large volumes of solvent have to be separated from a relatively low boiling product.

Since 1,4-enals can be prepared by Claisen rearrangement of allyl vinyl ethers, we also examined this route, and in the event, aldehyde **80** was prepared conveniently, in acceptable yield, and on a relatively large scale (50-100g) by pyrolysis of 3-ethenyloxy-1-propene (**82**) (equation 3).[69] The latter was available by a slightly modified (see Experimental) literature procedure.[71]



82 **80** (3)

With aldehyde **80** in hand, it was possible to examine the aldol condensation with enone **79**.* In principle, the crossed aldol condensation of a metal enolate with an aldehyde can produce two diastereoisomers (equation 4).**



(4)

Diastereoselectivity has been observed for the aldol condensation under conditions of either kinetic or thermodynamic control.[72,73] Under thermodynamic control - usually higher temperatures and/or longer reaction times - where equilibration of the aldols is possible, the *threo*-product is normally favoured. Under conditions of kinetic control - low temperatures and short reaction times - where equilibration of the aldols is not possible, diastereoselectivity is often strongly dependent upon enolate geometry: the

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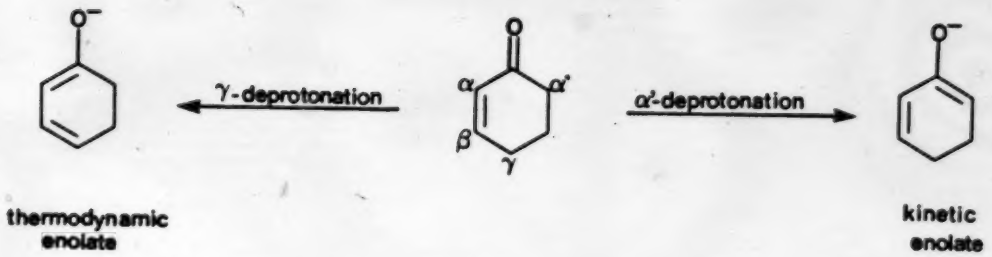
*For recent reviews of the aldol condensation see references 72, 73.

**These designations are not rigorous for all possible combinations of R_1, R_2 and R_3. One recently proposed convention[74] suggests that with the carbon backbone of the molecule drawn in an extended zig-zag fashion (as shown in equation 4), the *erythro*-configuration is designated as that where R_2 and OH bear a *gauche* relationship. The *threo*-configuration is that where these two groups exhibit an *anti* relationship.

Z-enolate usually favours the *erythro*-aldol, whereas the *E*-enolate favours the *threo*-product. This stereochemical dependence on enolate geometry has been rationalized by proposing a cyclic, six membered transition state, which assumes a chair conformation with as many substituents in equatorial positions as possible.[75]

A cyclic enone such as **79**, has two possible sites of deprotonation, the α'- and the γ-positions (Scheme 29).

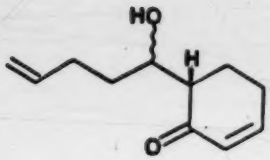
Scheme 29



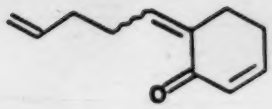
Deprotonation at the α'-position is usually faster (hence the site of kinetic deprotonation) but produces a cross-conjugated enolate. Deprotonation at the γ-position on the other hand, generates a fully conjugated enolate and is therefore usually the product of enolization under conditions of thermodynamic control.

Construction of the hexahydronaphthalene alcohol **103**, requires kinetic deprotonation and, therefore, the use of kinetic control for the aldol reaction.

In the event, kinetic deprotonation of enone **79** (LDA, -78°C) and condensation with aldehyde **80** (10 min, -78°C) followed by quenching of the reaction with saturated ammonium chloride solution, afforded aldol **83** in 56% yield together with some dehydration products **84** (19%).

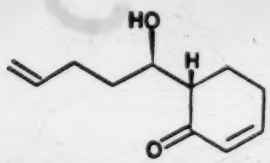


83

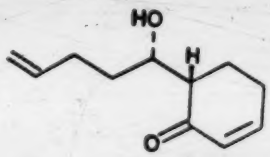


84

The aldol, which appeared to be homogeneous by TLC, proved to be a mixture of *erythro*- and *threo*-diastereoisomers (**83a** and **83b**): the ^{1}H NMR spectrum of aldol **83** showed that while many of the signals for the two diastereoisomers were overlapping, the carbinol proton signals were resolved (two multiplets at δ 4.20 and 3.92 in a ratio of approximately 1:1). An interesting observation concerning this reaction was that, while quenching the reaction with aqueous ammonium chloride afforded almost equal amounts of the two diastereoisomers, quenching with glacial acetic acid afforded the same two isomers in a ratio of approximately 2:1 in favour of that having its carbinol resonance at δ 3.92.



83a



83b

Since the enolate derived from a six membered ring ketone must have *E*-geometry, and because this aldol reaction was performed under conditions of kinetic control, the major product (from the acetic acid quenched reaction) is predicted to be the *threo*-diastereoisomer (**83b**). Evidence in favour of such an assignment was obtained on the basis of the following considerations.

β-Hydroxy-ketones in non-polar aprotic solvents, are thought to exist in intramolecularly hydrogen bonded conformations, with the maximum number of substituents disposed equatorially, as shown in Figure 2.[76] The coupling constant (J)

between the methine, and carbinol protons is usually larger (typically 6-9 Hz) for the *threo*-isomer, where these protons bear a *trans*-diaxial relationship, than for the *erythro*-compound (typically 2-4 Hz) where these protons are gauche.[76]

Figure 2

The carbinol proton signals at δ 4.20 and 3.92 in the NMR spectrum of aldol **83** simplified, upon D_2O exchange, to what appeared to be two doublets of triplets with J = 9.6, 3.2 Hz and 3.3, 7.5 Hz respectively. Irradiation of the methylene protons (H-2), however, caused these signals to collapse further to two doublets, J = 3 Hz for the signal at δ 4.20, and J = 7.3 Hz for the signal at δ 3.92. These data suggest, therefore, that the major product from the aldol condensation was that with *threo* stereochemistry and that the minor isomer has, the *erythro* configuration.

There are in the literature, however, cases where J *erythro* is found to be larger than J *threo*.[77] An alternative means of identifying aldol diastereoisomers has been described recently.[78] The ^{13}C NMR spectra of a large number of diastereoisomeric β-hydroxycarbonyl compounds were examined and empirical observations were made which are of value for assigning stereostructures. For α-methyl-β-hydroxycarbonyl systems (Figure 3) the chemical shifts of the methyl, methine, and carbonyl carbons were found to be the most diagnostically useful. For all three cases, upfield shifts were observed for the *erythro*-compound relative to the *threo*-isomer (Table 1). The origin of this effect was proposed to be due to differences in steric interactions in the preferred chair conformations (Figure 2) of the two intramolecularly hydrogen bonded isomers.

Figure 3

erythro threo

Table 1

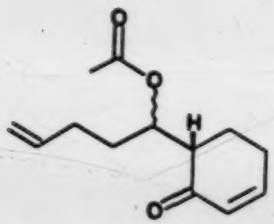
^{13}C NMR Chemical Shifts (δ)

of Some α-Methyl-β-Hydroxyketones

	carbinol	methine	methyl
erythro-	71.6-78.1	38.6-53.8	7.6-12.9
threo-	74.0-82.5	40.8-55.2	10.9-17.9

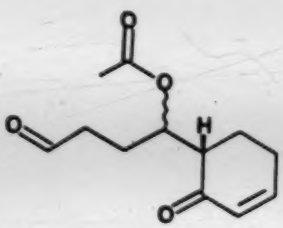
For the aldols **83**, the methine carbon resonances coincided (δ 51.3) but the carbinol resonance for the minor isomer (acetic acid quench) was upfield (δ 68.4) of the corresponding signal for the major component (δ 70.5). These data, therefore, are consistent with the assignment of *threo*-stereochemistry to the major product. The assignments must, however, be considered tentative at this stage; they were proven correct only by eventual conversion of the aldol mixture **83** to bicyclic alcohol **103b** and its C-1 epimer **103a** (where the rigid structures permit an unambiguous stereochemical assignment by NMR).

The next step for conversion of aldol **83** to compound **103** was protection of the hydroxyl. Treatment of **83** with pyridine and acetic anhydride at room temperature afforded acetate **85** in 90% yield.



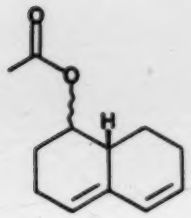
85

Exposure of acetate **85** as a solution in methanol-dichloromethane (1:1) to ozone at -78°C, followed by reductive workup (dimethyl sulfide, room temperature) then gave aldehyde **86** in 74% yield.



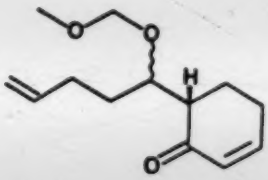
86

With this compound in hand, we were in a position to try the carbonyl coupling leading to the hexahydronaphthalene unit. It has been demonstrated that many sizes of ring can be formed by titanium induced intramolecular coupling of dicarbonyl compounds under conditions of high dilution.[10,11] However, when enone aldehyde **86** was treated with $TiCl_3$-Zn(Cu) couple, by the procedure desribed in the literature,[11] little, if any, of the desired bicyclic compound **87** was obtained. We considered it likely that this was due to the unsuitability of the acetate protecting group for a reaction involving low valent titanium, because of the highly reducing nature of this reagent.[11]



87

A number of attempts were made to protect the alcohol functionality of **83** as a methoxymethyl ether, but under a variety of reaction conditions, none of the desired product **88** was detected.



88

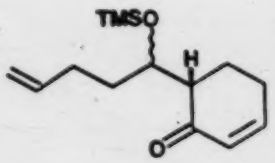
When the aldol condensation to form **83** was quenched at -78°C with methoxymethyl chloride , no new products were detected (TLC), at that temperature. Upon warming to 25°C, no aldol remained, only the dehydration product **84** could be isolated (27% yield).

When aldol **83** was treated with a mixture of methoxymethyl chloride, triethylamine and a catalytic amount of 4-(*N*,*N*-dimethylamino)pyridine, only the starting material and dehydration product **84** were detected, even after a four day reaction period at room temperature.

Non-basic conditions were also examined. Aldol **83** was treated with methylal and phosphorus pentoxide at room temperature in chloroform, according to the literature procedure.[12] After five days some of the aldol remained, and the only major product was **84**.

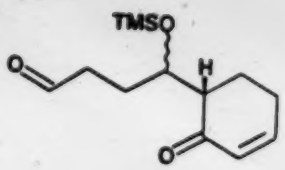
Attempts to prepare various silyl ethers were much more successful. When aldol **83** was treated with a mixture of triethylamine and chlorotrimethylsilane in ether, it was

slowly converted to trimethylsilyl aldol **89**. After 12 h at room temperature, and a prolonged period (22 h) at reflux, the reaction had proceeded only to approximately 50% conversion. However, if a catalytic amount (20 mol %) of 4-(*N*,*N*-dimethylamino)pyridine (DMAP) was added, the reaction was complete after an overnight period at room temperature, and proceeded in high yield (93%).



89

Ozonolysis of trimethylsilyl aldol **89** under the conditions used successfully to prepare enone aldehyde **86** (methanol-dichloromethane solvent, dimethyl sulfide workup) resulted in total decomposition of **89**. None of the desired product **90** could be isolated.

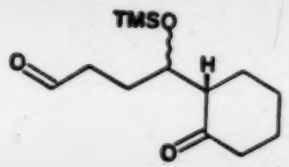


90

A variety of ozonolysis conditions were examined. When the reaction was repeated with trimethylphosphite as the reducing agent, total decomposition of the starting material was again observed. If, however, pure methanol was employed as the solvent, in place of 1:1 methanol-dichloromethane, and trimethylphosphite was used as reducing agent, then aldehyde **90** was isolable in yields ranging from 43% to 74% (average 61% over five experiments).

Catalytic hydrogenation is a particularly mild reaction and it was also examined for reduction of the initial ozonolysis products. A solution of trimethylsilyl aldol **89** in ethyl acetate was treated with ozone (-78°C), then stirred at room temperature with 5%

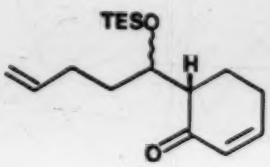
palladium on carbon under an atmosphere of hydrogen. Two substances were isolated by chromatography: the desired enone aldehyde **90** (37% yield) and keto aldehyde **91** (15%).



91

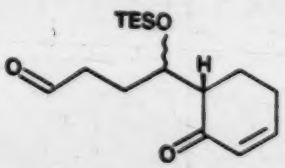
This undesired overreduction could be avoided by use of Lindlar's catalyst;[44] however, enone aldehyde **90** was still produced in only modest yield (38%).

The triethylsilyl (TES) and *tert*-butyldimethylsilyl (TBDMS) protecting groups were also examined for aldol **83**. Triethylsilyl aldol **92** was prepared (85%) by treatment of aldol **83** with chlorotriethylsilane in pyridine.[33]



92

Ozonolysis of **92** under a variety of conditions (Table 2) gave no better yields of aldehyde **93** than with the trimethylsilyl protecting group.



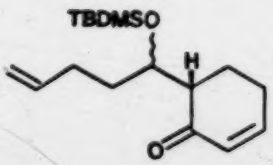
93

Table 2

Ozonolysis of TES Aldol 92

solvent	reducing agent	yield of **93**
ethyl acetate	H_2 / Lindlar's catalyst	42%
methanol	dimethyl sulfide	49%
methanol	trimethylphosphite	53%

The *tert*-butyldimethylsilyl aldol **94** was prepared (57%) using *tert*-butylchlorodimethylsilane and imidazole in DMF,[44] but proved no better in the ozonolysis step.

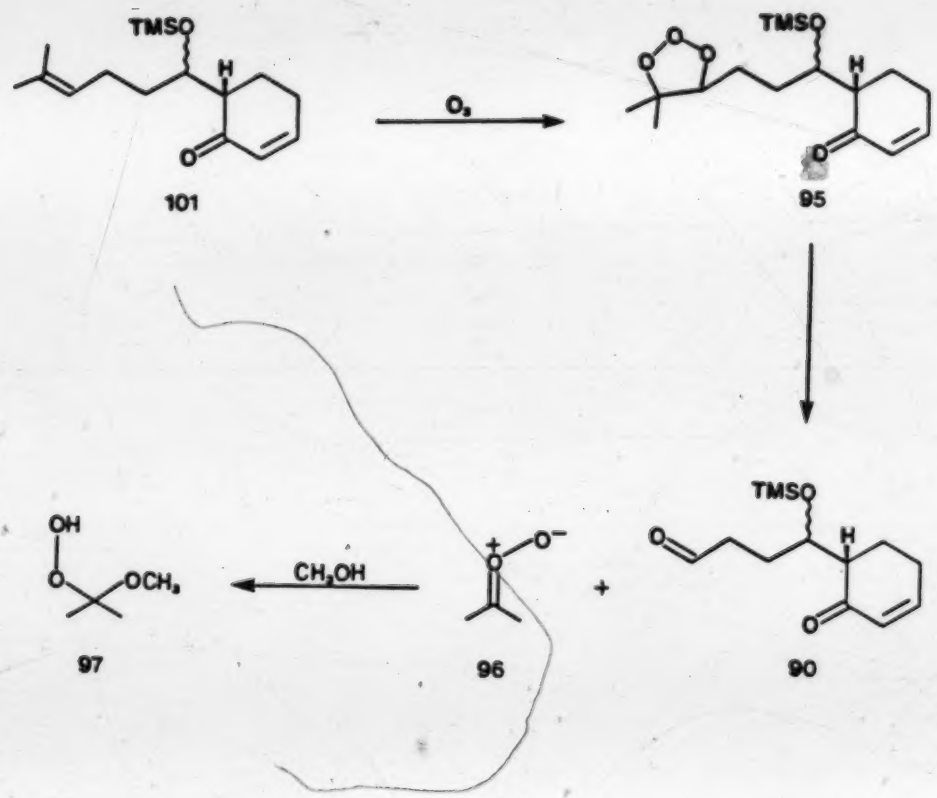


94

A modification to the vinyl group was examined as a means of improving the yield in the ozonolysis.* Ozone is thought to be an electrophilic reagent, since kinetic studies of its addition to various substituted olefins show that substituents generally increase the rate of attack if they are electron releasing, and decrease the rate if electron withdrawing.[87,88] If ozonolysis of the enone carbon-carbon double bond competes with ozonolysis of the vinyl group of **89**, then substitution of the vinyl group should make this process less competitive. Another consideration is that decomposition of a primary ozonide to a carbonyl component and a carbonyl oxide occurs in such a way that the carbonyl component is derived from the less substituted end of the original double bond.[89] For these reasons, ozonolysis of **101** would be expected to result in decomposition of the primary ozonide **95** to carbonyl oxide **96** and aldehyde **90** (Scheme 30). If the ozonolysis were carried out in methanol, the carbonyl oxide would be trapped as a methoxy hydroxyperoxide **97**.[89] Under these circumstances, aldehyde **90** is a direct product of the

*For a review of ozonolysis, see reference 88.

Scheme 30

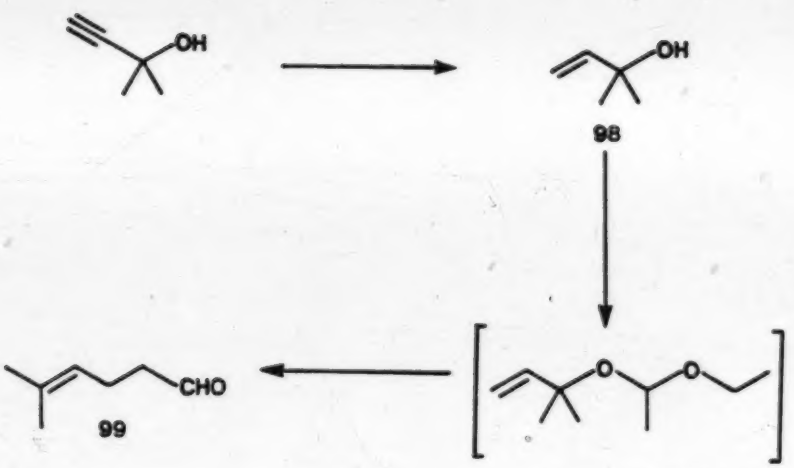


ozonolysis and not the result of subsequent reduction. In principle, it should be unnecessary to reduce the ozonolysis mixture in order to obtain **90**. Even if reduction were performed (to decompose any peroxidic byproducts present), **90** would not be involved, so that if reduction of the ozonolysis products is responsible for the lower yields obtained in previous reactions, this problem might be circumvented in the case of **101**.

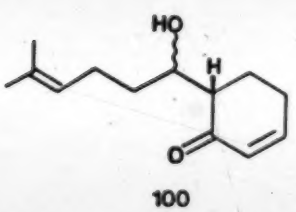
Compound **101** was prepared in two steps from 2-cyclohexenone (**79**) and 5-methyl-4-hexenal (**99**). The latter is a known substance and it was made by the literature route[90,91] shown in Scheme 31.

Aldol condensation of enone **79** with aldehyde **99** in the usual fashion gave **100** in 43% yield as a mixture of two diastereoisomers in a ratio of about 2.3:1.

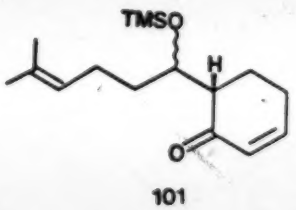
Scheme 31



Protection of the alcohol as its trimethylsilyl ether afforded **101** in 74% yield.



100



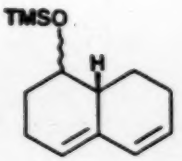
101

This compound did, in fact, prove to be a better substrate for ozonolysis. Over four attempts, ozonolysis (methanol, -78°C) followed by reductive workup (trimethylphosphite) gave aldehyde **90** in yields ranging from 62% to 87% (average 77%). However, the aldol condensation and protection steps proceeded in poorer yields and thereby made this process less efficient overall than the route involving 4-pentenal (**80**).

An alternative reaction used to cleave carbon-carbon double bonds is the Lemieux-Johnson oxidation.[92] Treatment of the trimethylsilyl aldol **89** under the reported conditions ($NaIO_4$, catalytic OsO_4, 1:1 H_2O-ether) however, resulted in complete decomposition of the starting material and no detectable (TLC) amount of the desired

aldehyde **90**.

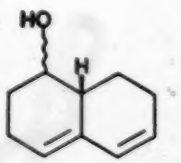
With enone aldehyde **90** in hand, it was possible to examine once again the critical ring closure. Treatment of **90** with low valent titanium according to the literature procedure,[91] gave compound **102** in 55% yield, after chromatography and distillation.



102

Some aspects of this reaction are worth noting. The reported procedure involves high dilution conditions (slow addition of the substrate by motor driven syringe pump to the reducing agent) and was used to prepare four to sixteen membered rings.[90,91] Since a six membered ring is formed in our reaction and should be an entropically favoured process, non-high dilution conditions were examined.. The substrate **90** (as a solution in dry DME) was added in one portion to the titanium reagent; however, a lower yield (36%) of cyclized product **102** resulted.

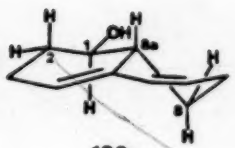
The workup procedure described for this reaction calls for filtration of the crude mixture through Florisil. This appears to be critical for retention of the trimethylsilyl protecting group. When the reaction mixture was instead filtered through Celite, which presumably does not retain all of the titanium species, only a mixture of alcohols **103** was obtained. Furthermore, this desilylated product was obtained in better yield (74%) than the trimethylsilyl derivative **102**. Alternatively, **102** could be desilylated by treatment with excess fluoride ion[93] to give alcohols **103** in 81% yield.



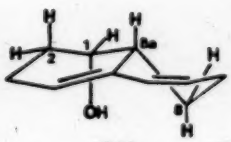
103

Because these bicyclic compounds possess relatively rigid structures, it was possible to make unambiguous stereochemical assignments by NMR. In the 200 MHz ^{1}H NMR spectrum of the mixture of **103a** and **103b**, while many of the signals for the two diastereoisomers overlapped, the signals for the carbinol (H-1) protons were clearly resolved at δ 3.99 and δ 3.49 for the major and minor isomers (originating from the acetic acid quenched aldol reaction), respectively. Upon D_2O exchange, the signal at 3.99 appeared as a broad singlet ($W_{1/2}$ = 9 Hz) whereas the signal at δ 3.49 appeared as a multiplet ($W_{1/2}$ = 35 Hz). On comparison of the stereochemistry of compounds **103a** and **103b** (shown in Figure 4), it is seen that the carbinol proton of **103a** should have two large couplings because of its *trans*-diaxial relationship to both H-8a and H-2 axial, and one small coupling to H-2 equatorial because of its *cis*-relationship to this proton. The carbinol proton of **103b** however, would have only relatively small couplings because of its *gauche*-relationship to all of these protons. On the basis of such expectations, the isomer with its carbinol signal at δ 3.99 and showing no large couplings (the major isomer from the acetic acid quenched aldol reaction) was assigned structure **103b**. The isomer with its carbinol signal at δ 3.49 and showing large couplings must, therefore, have structure **103a**.

Figure 4



103a



103b

Further evidence for this stereochemical assignment was found in the ^{13}C NMR spectrum of the mixture. The most diagnostic feature was the fact that C-1 in the major isomer showed a chemical shift at δ 68.4 whereas the corresponding signal for the minor

isomer appeared at δ 73.0. These chemical shifts are consistent with those for carbon atoms in a cyclohexane ring bearing an axial and equatorial hydroxyl group, respectively. For example, *cis*-4-*tert*-butylcyclohexanol (**104**) where the hydroxyl group is axially oriented shows a chemical shift of δ 65.0 for the carbinol carbon whereas the corresponding *trans*-isomer **105**, with the hydroxyl group equatorially disposed, shows a chemical shift of δ 70.4.[94] These observations also suggest that the major and minor isomers of the mixture of bicyclic alcohols have structures **103b** and **103a** respectively.

104

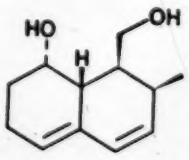
105

This conclusion also provides unambiguous evidence that the aldol condensation used to prepare **83** favoured the *threo*-aldol **83b** over the *erythro*- aldol **83a** when acetic acid was employed to quench the reaction.

Having demonstrated the viability of our annellation approach, we used the same sequence to construct the bicyclic portions of Mevinolin and Compactin.

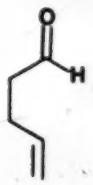
B. Synthesis of the Hexahydronaphthalene Portion of Compactin

Our target molecule, embodying the four chiral centers present in the lower portion of Compactin, was diol **127b**. This compound also possesses the functionality we considered necessary for elaboration into the natural product.

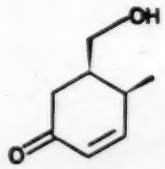


127b

By our annellation sequence, diol **127b** would be prepared from 4-pentenal (**80**) and the suitably protected enone alcohol **118**.

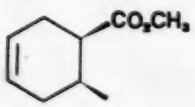


80

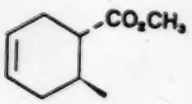


118

An appropriate enone (**120**) was prepared from *cis*-acid **114** by the route outlined in Scheme 32. The acid is a known compound which had been made by isomerization of readily available *trans*-acid **106** (Scheme 33).[93]* The latter, which is the product of a Diels-Alder reaction between butadiene and *E*-crotonic acid, was converted to its *sec*-butyl ester (**107**) via the acid chloride. When ester **107** was hydrolysed with potassium hydroxide in ethylene glycol, a mixture of *cis*- and *trans*-acids (**114** and **106**) in approximately equal proportions was obtained. In the literature procedure,[93] the mixed acids were separated chromatographically, but we found it much more convenient on a large scale, to separate the derived methyl esters (**108** and **109**)[96] by spinning-band distillation.



108



109

The esters were easily prepared** by treatment of the acids with dimethyl sulfate and potassium carbonate. Hydrolysis of *cis*-ester **108** to the desired *cis*-acid **114** could be accomplished (KOH, methanol-water, room temperature, 92%) without isomerization back to *trans*-acid **106**.

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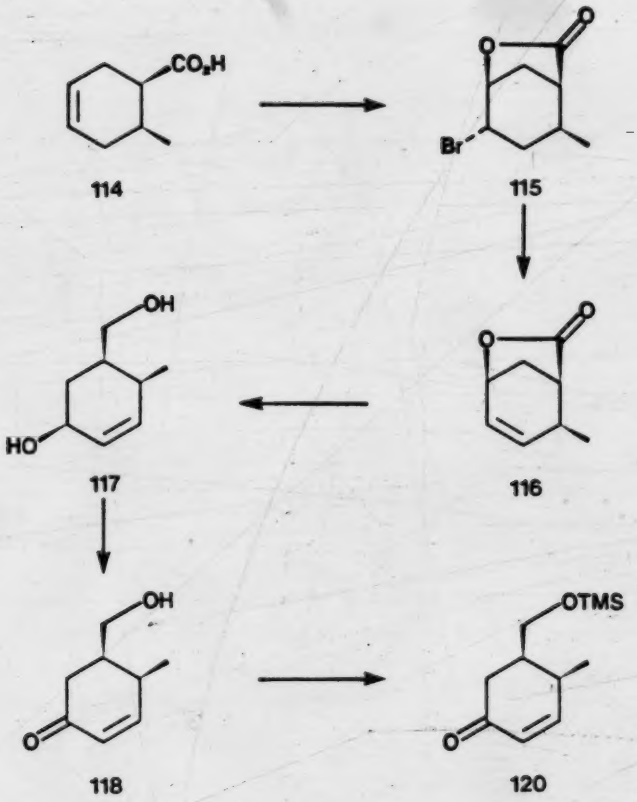
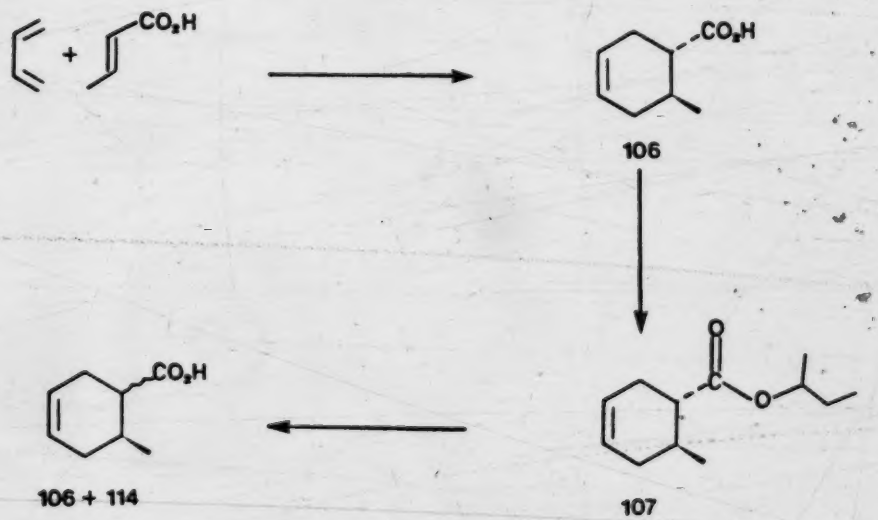
*This work was done by C. F. Evans.[67,68]
**The esters were prepared by C. F. Evans.[67,68]

Scheme 32



114 115 116 117 118 120

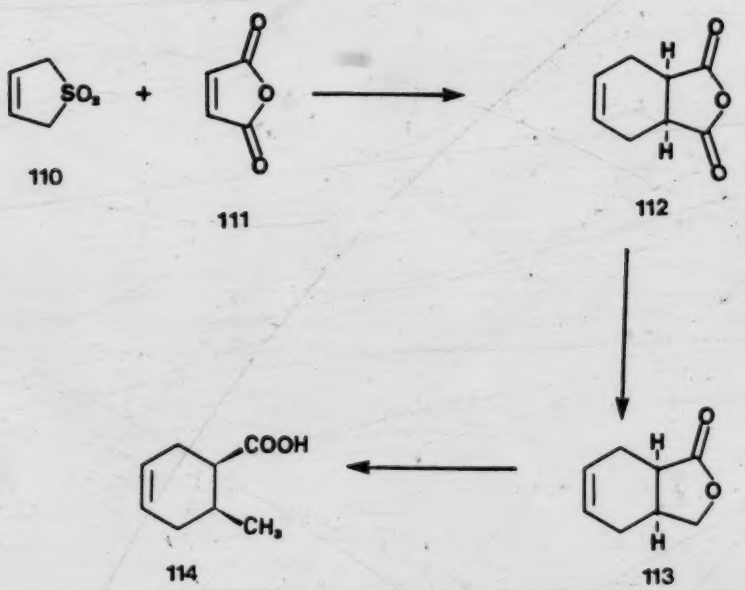
Scheme 33



106 107 106 + 114

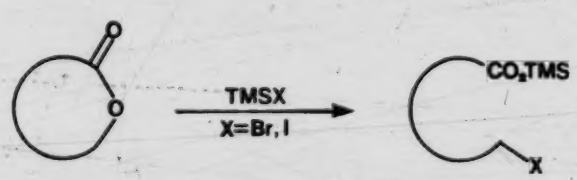
We also examined a much shorter route (summarized in Scheme 34) to *cis*-acid **114**.

Scheme 34



Cis-anhydride **113** is commercially available (Aldrich), or was readily prepared by the Diels-Alder reaction of 3-sulfolene (**110**) and maleic anhydride (**111**).[97] Partial reduction of **112** to the known lactone **113** was accomplished (67%) by a literature procedure, using lithium aluminum hydride at low temperature (-55°C).[98]

Lactones have been shown to undergo ring opening upon treatment with bromo- or iodotrimethylsilane to give ω-bromo- or iodo-trimethylsilyl esters (Equation 5).[99]



(5)

Alkyl bromides and iodides in particular can be reduced selectively in the presence of a variety of other functional groups by treatment with tributyl- or triphenyltin hydride.[100]

By a combination of these two reactions, lactone **113** was converted into *cis*-acid **114**. Lactone **113**, as a solution in dry benzene, was treated first with iodotrimethylsilane and then with triphenyltin hydride. Workup, involving hydrolysis of the trimethylsilyl ester (aqueous potassium fluoride), and distillation, gave *cis*-acid **114** in 43% yield from **113**. This one flask procedure avoided the necessity of isolating a hydrolytically unstable trimethylsilyl ester. However, the low overall yield, and the inconvenience and expense involved in the use of iodotrimethylsilane and triphenyltin hydride on a large scale, render our modified literature method preferable, and we routinely made large (> 100 g) batches of **114** in this way.

Conversion of *cis*-acid **114** to protected enone alcohol **120** was straightforward, and proceeded according to the sequence of transformations previously outlined in Scheme 32.

The first step involved conversion of acid **114** to bromolactone **115**. In conventional bromolactonizations, an alkali metal salt of an unsaturated acid is treated with bromine.* In this fashion, *cis*-acid **114** was dissolved in aqueous sodium hydroxide and treated with a solution of bromine in dichloromethane.[102] After workup, a white crystalline substance was obtained in 59% yield. The IR spectrum showed a carbonyl absorption (1795 cm^{-1}) characteristic of a δ-lactone. Attempts were made to improve the yield of this reaction: modifying the base (aqueous NaOH or $NaHCO_3$) or the mode of addition of bromine (neat, or as a solution in CH_2Cl_2), varying the reaction time or reagent proportions, all resulted in similar product yields (51-65%).

Halolactonization has also been carried out under conditions of the Hunsdiecker reaction.[101] Accordingly, *cis*-acid **114** was converted into its silver salt, which was then suspended in DMF and treated with bromine.[103] An exothermic reaction occurred and lactone **115** was obtained in 78% yield (over the two steps). This sequence proved more efficient than direct halolactonization of the acid itself.

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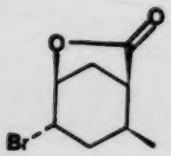
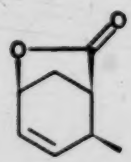
* For a recent review of halolactonization reactions, see reference 101.



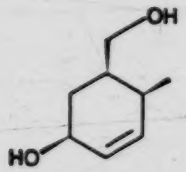
115

For the dehydrobromination of **115** to **116**, 1,5-diazabicyclo[4.3.0]non-5-ene was found to be effective provided it was used in a refluxing toluene.* Under these conditions, pure **116** was obtained in 84% yield.



116

Reduction of lactone **116** to diol **117** with lithium aluminum hydride proceeded smoothly and in high yield (92%).



117

Selective oxidation of the allylic alcohol of **117** was achieved with activated manganese dioxide[104] ($CHCl_3$, 3 h at room temperature) and produced enone alcohol **118** in 85% yield, together with a small amount (3%) of ketone **119**, a compound which arises from an intramolecular Michael addition.

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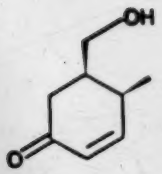
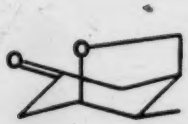
*Use of ether or benzene at reflux gave yields of 0% and 16% respectively.



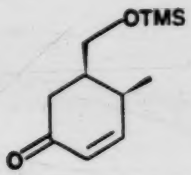
118



119

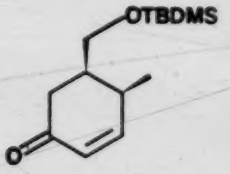
The course of this oxidation depended on the batch of manganese dioxide. With less active samples, longer reaction times were required, the yield of the desired product decreased, and the proportion of byproduct rose.*

Protection of the hydroxyl group of **118** as its trimethylsilyl ether proceeded smoothly, under standard conditions, to afford **120** (98%).



120

The *tert*-butyldimethylsilyl ether **121** was also prepared (TBDMSCl, imidazole, DMF)[16] but only in moderate yield (57%).

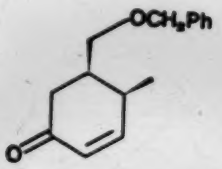


121

Attempts to make the benzyl protected enone alcohol **122** under conditions normally employed for this transformation (NaH, $PhCH_2Br$, THF) produced very complex

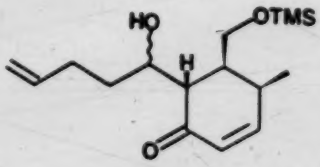
*For example, in one experiment, the reaction required 8 h to go to completion, and a 72% yield of enone **118** was obtained together with 8% of **119**.

mixtures. This result was not too surprising in view of the tendency of enone alcohol **118** to undergo intramolecular Michael addition, even under the neutral conditions of the manganese dioxide oxidation.



122

With protected enone alcohol **120** in hand, we proceeded to investigate its aldol condensation with 4-pentenal (**80**). Kinetic deprotonation of **120** and condensation with aldehyde **80** followed by quenching the reaction with aqueous ammonium chloride, afforded aldol **123** (85%) as two partially resolvable (TLC) diastereoisomers in a ratio of 1.6:1.



123

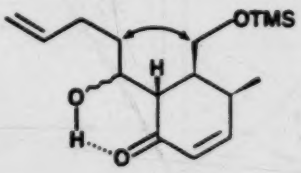
In contrast to the aldol condensation of 2-cyclohexen-1-one (**79**) with aldehyde **80**, this reaction showed no dependence of diastereoselectivity on the quenching agent. When glacial acetic acid was used, the same ratio (1.6:1) of diastereoisomers was obtained, although in marginally higher yield (88%). Also of interest was the fact that no dehydration products were isolated.

It was possible to separate these aldol diastereoisomers by flash chromatography,[105] and to establish that both were in fact the result of condensation from the less hindered face of the enone. The 200 MHz ^{1}H NMR spectrum of the major isomer showed the signal for H-8a as a doublet of doublets, J = 8, 5.5 Hz. Irradiation of the H-1

resonance caused the signal for H-8a to simplify to a doublet, J = 8 Hz. This establishes J-8,8a as 8 Hz and J-1,8a as 5.5 Hz for the major diastereoisomer. Similar experiments with the minor aldol showed J-8,8a to be 10.5 Hz and J-1,8a, 5.3 Hz. The relatively large coupling constants J-8,8a for the two diastereoisomers, suggest a *trans*-diaxial relationship between H-8 and H-8a. Hence H-8a has the stereochemistry shown (compound **123**) and aldol condensation must have occurred, as expected, from the less hindered face of the enone.

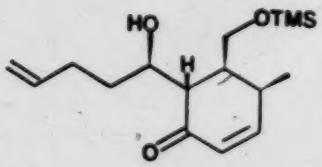
The similar, and intermediate J-1,8a coupling constants for the two diastereoisomers do not allow assignment of relative stereochemistry at this stage. Indeed, the J values suggest that these compounds do not exist in intramolecularly hydrogen bonded conformations (Figure 5).

Figure 5

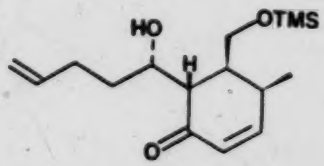


This may be a consequence of the destabilizing effect of bringing the alkenyl side chain closer to the trimethylsilylcxymethyl group as required for intramolecular hydrogen bonding (Figure 5). A similar explanation may account for the decreased tendency of aldol **123** to undergo dehydration, since such a reaction would lower the dihedral angle between the side chain and the bulky trimethylsilyloxymethyl appendage (Figure 6).

As was previously discussed, under conditions of kinetic control, *Z*-enolates usually favour *erythro*-aldol products, and *E*-enolates favour the *threo*-isomer.[72,73] On the basis of these considerations, the major aldol from this reaction is predicted to be the *threo*-aldol **123b**.

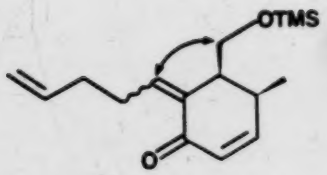


123a



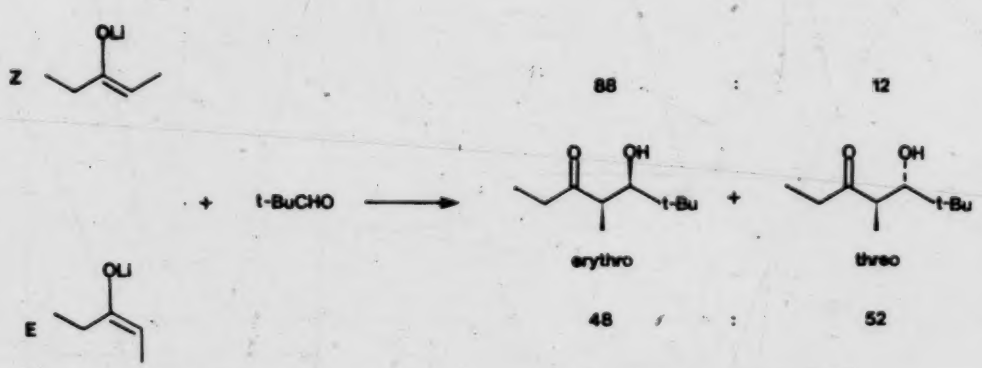
123b

Figure 6

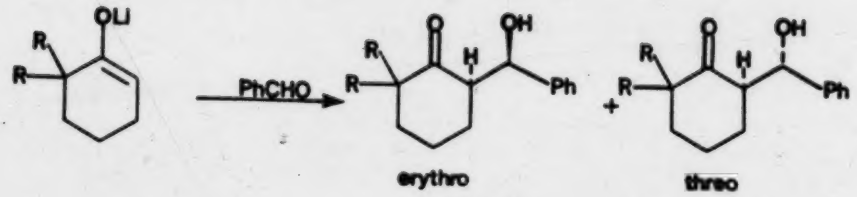


Since the *threo*-isomer is that required for conversion to the hexahydronaphthalene unit of Compactin, an attempt was made to improve the diastereoselectivity of the reaction. It has been observed that *E*-enolates are often less diastereoselective in aldol condensations than the corresponding *Z*-isomer (see, for example Scheme 35)."

Scheme 35



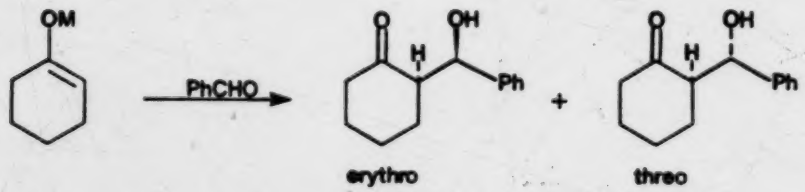
The *E*-enolates derived from cyclohexanones, are particularly unselective (equation 6).[106]



(6)

R	*erythro*	*threo*
H	48	52
CH_3	13	87

A study of the various metal counter-ions has demonstrated that the highest level of *threo*-diastereoselectivity is usually obtained with a boron enolate (equation 7).[10]



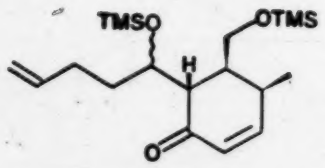
(7)

M	*erythro*	*threo*	ref.
Li	48	52	106
$AlMe_2$	50	50	108
$B(C_3H_6)(C_6H_{13})$	4	96	107

We therefore examined the boron mediated aldol condensation of enone **120** with aldehyde **80**. The lithium enolate was trapped with chlorotriethylborane,[109] and the resulting cyclohexenyloxyborane was condensed with 4-pentenal (**80**). Oxidative workup ($(CH_3)_3N$-O)[123] and chromatography afforded, in low yield (37%), what appeared to be a partially resolvable (TLC) mixture of two diastereoisomers. High field ^1H NMR measurements, however, demonstrated that the product was a much more complex mixture, and so this approach was abandoned.

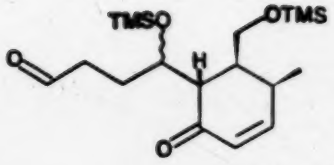
Since it was not possible at this stage to assign unambiguous relative configurations to the two aldol diastereoisomers, the mixture of isomers, and each individual isomer, were separately carried through the synthesis.

Protection of the aldol as its trimethylsilyl ether **124** in the usual fashion gave good yields of product (84%). The material proved however to be extremely unstable towards hydrolysis and a completely non-aqueous workup had to be employed. This trimethylsilyl ether **124** was also very sensitive to silica gel chromatography: some decomposition was observed even on TLC analysis. The high yields of product achieved after chromatography were probably possible only because of the use of the flash chromatography technique,[105] in which the compounds stay on the column for only a short time.



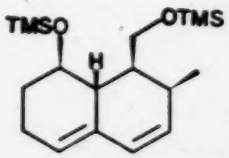
124

Attempted ozonolysis of **124** using the conditions found to be most effective for compound **89** in the model series (O_3 in methanol, -78°C; trimethylphosphite workup) resulted in complete decomposition, and so a variety of conditions were again examined. Ozonolysis in methanol, followed by workup with dimethyl sulfide similarly resulted in product decomposition. Catalytic hydrogenation over Lindlar's catalyst, or dimethyl sulfide workup after ozonolysis in dichloromethane, appeared to slowly reduce the ozonide to the desired aldehyde **125**, whereas workup with borane-dimethylsulfide complex or with tributylphosphine gave no detectable (TLC) amount of aldehyde. Ozonolysis in dichloromethane followed by reductive workup with triphenylphosphine, proved to be most effective for preparation of aldehyde **125**. The reaction was somewhat capricious however, and gave variable yields, generally between 55% and 86% (average 69% over 9 experiments). These aldehydes were quite unstable and decomposed to white, insoluble solids within a few days, even when stored below 0°C under an atmosphere of argon.

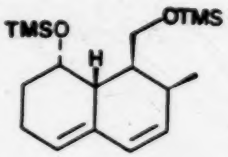


125

Intramolecular titanium induced carbonyl coupling[90,91] of enone aldehyde **125** proceeded in the same fashion as with model compound **90**. When the crude reaction mixture was filtered through Celite, the cyclized product was isolated as a mixture of diastereomeric diols **127a** and **127b** in 73% yield.

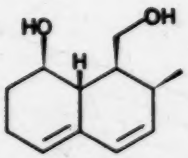


126a

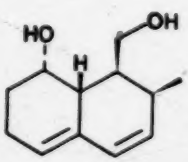


126b

Alternatively, if the reaction mixture was filtered through a pad of Florisil, the product was isolated as a mixture of bistrimethylsilyl ethers **126a** and **126b** (85%) which could be desilylated (83%) to the diols **127a** and **127b** by treatment with fluoride ion.[93]



127a



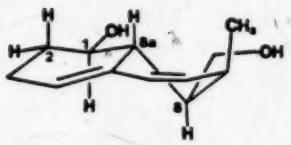
127b

The diols could be separated chromatographically. As expected, the major isomer proved to be identical to the product obtained by carrying the major aldol isomer (from **123**) through the same sequence of reactions. Similarly the minor isomer from the diol

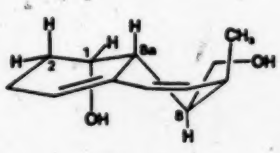
mixture was identical to the product obtained from the minor aldol diastereoisomer (of **123**).

Based upon their mode of formation, the two diastereoisomeric alcohols were expected to possess the structures shown in Figure 7.

Figure 7



127a



127b

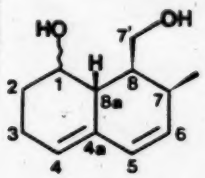
Compound **127a** is derived from the *erythro*-aldol **123a** and compound **127b** is derived from the *threo*-aldol **123b**.

In order to assign these structures to the individual product isomers and to establish unambiguously that the compounds do possess the relative stereochemistries shown, a series of extensive NMR experiments was performed. Summaries of the assigned ^{1}H NMR spectra of the major and minor isomers of **127** are shown in Tables 3 and 4 respectively. The assignments for H-1, H-4, H-5, H-6, H-7' and CH_3 follow from a consideration of the chemical shifts and coupling patterns of these signals. The assignments for the hydroxyl protons were made after D_2O exchange, while those for H-2, H-3, H-7, H-8 and H-8a were made using selective proton decoupling in conjunction with the addition of enough Eu(fod)$_3$-d_{30} to the sample, to resolve these signals. In the case of the major isomer, some measurements were carried out in the presence of trichloroacetyl isocyanate. These last experiments also permitted determination of diagnostically important coupling constants which are summarized in Table 5.

For both isomers, J-8,8a was large and J-7,8 was small. These magnitudes suggest, for both compounds, a *trans*-diaxial relationship between H-8 and H-8a and a

Table 3

^{1}H NMR Data for the Major Isomer of 127

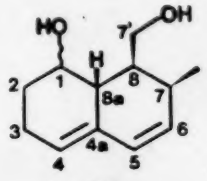


127

δ	Multiplicity (J)	Integration	Assignment
5.96	d (9.5 Hz)	1H	H-5
5.68	dd (9.7, 6Hz)	1H	H-6
5.61	br s	1H	H-4
4.25	br s	1H	H-1
3.84	dd (10, 8.5Hz)	1H	H-7'
3.22	br d (10 Hz)	1H	H-7'
2.88	br s	1H	OH
2.47	m	2H	OH, H-7
2.34	dm (11Hz)	2H	H-3ax, H-8a
2.14	dtm (17.7, 5.3 Hz)	1H	H-3eq
2.00	m	2H	H-8, H-2ax
1.73	m	1H	H-2eq
0.88	d (6.5 Hz)	3H	CH_3

Table 4

^{1}H NMR Data for the Minor Isomer of 127



127

δ	Multiplicity (J)	Integration	Assignment
5.97	d (9.8 Hz)	1H	H-5
5.65	dd (9.5, 5.8 Hz)	1H	H-6
5.51	br s	1H	H-4
4.11	br s	1H	OH
4.02	br s	1H	OH
3.88-3.71	m	3H	H-1, 2H-7'
2.33	m	2H	H-7, H-8a
2.24	m	2H	2H-3
2.01	dq (11.8, 3.3 Hz)	H	H-2eq
1.78-1.63	m	2H	H-8, H-2ax
0.94	(d, 7 Hz)	3H	CH_3

Table 5

Diagnostically Important Coupling Constants

For the Major and Minor Isomers of 127

coupling constant	major isomer	minor isomer
J-1,8a	small	11 Hz
J-7,8	<7 Hz	*ca.* 5 Hz
J-8,8a	12 Hz	11 Hz

cis-relationship between H-7 and H-8. This conclusion therefore establishes the stereochemistry shown in **127** for C-7, C-8 and C-8a. Proton H-1 in the major isomer has no large coupling, whereas J-1,8a in the minor isomer is large. These data suggest that the major isomer has H-1 equatorially disposed (**127b**) and that the minor isomer has H-1 in an axial orientation (**127a**).

Further evidence for the stereochemistry at C-1 was obtained from the ^{13}C NMR spectra of the two isomers. The assigned ^{13}C NMR spectral data for the major and minor isomers of **127** are shown in Table 7.

Assignments for the minor isomer follow from a consideration of the chemical shift and multiplicity of the observed signals, and from selective ^{1}H decoupled ^{13}C NMR spectra, the results of which are summarized in Table 6.

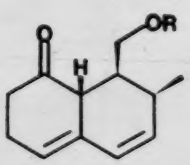
Assignments for the major isomer also follow from chemical shift and multiplicity considerations as well as by analogy to the minor isomer.

As with model compound **103**, C-1 of the major isomer has a chemical shift (δ65.3) indicative of a cyclohexane carbon bearing an axial hydroxyl group.[94] By contrast, the corresponding signal for the minor isomer is at a chemical shift (δ71.3) characteristic of a cyclohexane carbon bearing an equatorial hydroxyl.[94]

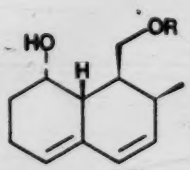
On the basis of these NMR data, the major isomer has the relative stereochemistry defined by the formula **127b**, and the minor isomer the stereochemistry shown in **127a**.

This conclusion also indicates that the aldol condensation used to form **123** favoured the *threo*-aldol **123b** over the *erythro*-aldol **123a**.

The major product of the sequence (**127b**) possesses the correct relative configuration of the four asymmetric centers in the hexahydronaphthalene portion of Compactin. It has been reported in the literature that ketones such as **128** can be reduced stereoselectively to alcohols **129** possessing the desired C-1 α-stereochemistry, with either L-Selectride (R = TBDMS)[61] or K-Selectride (R = $CH_2CH_2OCH(CH_3)OCH_2CH_3$)[60].



128



129

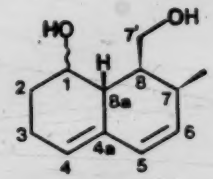
Table 6

Results of Selective ^{1}H Decoupled ^{13}C NMR Spectra of the Minor Isomer of 127

Proton Decoupled	^{13}C Signal (δ) Enhanced
H-3	132.8
H-4	127.9
H-5	124.6
H-2, H-8	45.1, 32.3
H-7, H-8a	41.9, 34.8

Table 7

^{13}C NMR Shifts (δ) for the Major and Minor Isomers of Compound 127



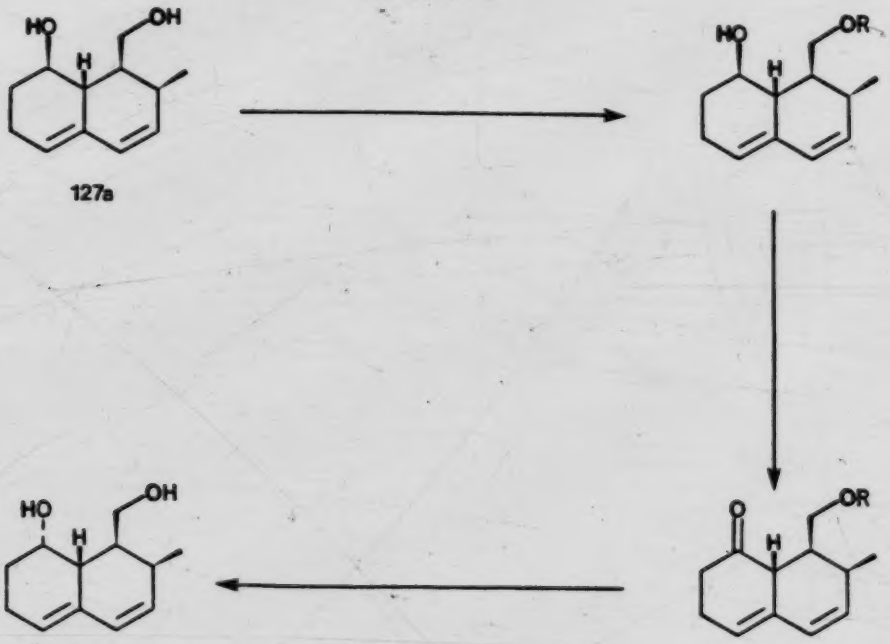
127

Carbon	Major Isomer	Minor Isomer
1	65.3 (d)	71.3 (d)
2	28.6 (t)	32.3 (t)
3	20.4 (t)	25.0(t)
4	123.9 (d)	124.6 (d)
4a	133.6 (s)	135.3 (s)
5	128.6 (d)	127.9 (d)
6	132.5 (d)	132.8 (d)
7	33.3 (d)	34.8 (d)
8	40.6 (d)[a]	45.1 (d)
8a	38.6 (d)[a]	41.9 (d)
7'	65.5 (t)	66.1 (t)
CH_3	14.8 (q)	15.3 (q)

[a] These assignments may be interchanged.

In principle, therefore, it should be possible to adjust the stereochemistry of the minor isomer **127a** at this stage, by a route (Scheme 36) involving selective protection of the primary (C-7') alcohol, oxidation of the secondary (C-1) alcohol to a ketone, and stereoselective reduction, followed by deprotection to afford **127b**.

Scheme 36



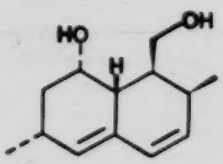
127a

127b

Having completed the synthesis of a compound representing the hexahydronaphthalene portion of (±)-Compactin, we turned our attention to the corresponding portion of Mevinolin.

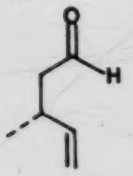
C. Preparation of the Hexahydronaphthalene Portion of Mevinolin

Mevinolin has an additional chiral center (C-3) when compared to Compactin, so that our target molecule was now diol **138a**.

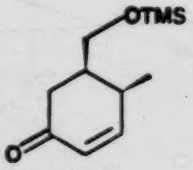


138a

This was to be constructed from enone **120** and the chiral aldehyde **135**.



135

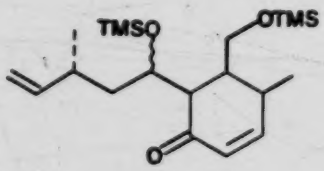


120

This aldehyde was prepared in our laboratory* by the route outlined in Scheme 37.

Optically active (S)-Citronellol (**130**) was protected as its acetate **131** and then ozonized using a reductive workup followed by Jones oxidation. The resulting acid **132**, obtained in 60% overall yield, was treated with lead tetraacetate and cupric ion[111] to give alkene **133** in 72% yield (90% based on non-recovered starting material). Hydrolysis of the acetate and Collins oxidation completed the route to aldehyde **135**.**

Kinetic deprotonation of enone **120** and condensation with chiral aldehyde **135** afforded (62%) an aldol product, which was directly protected as its trimethylsilyl ether under the usual conditions, to afford compound **136** (81%) as a mixture of four diastereoisomers.



136

Ozonolysis in dichloromethane (-78°C) followed by reductive workup with triphenylphosphine (60%) and cyclization using low valent titanium[80,81] afforded (67%) bistrimethylsilyl ether **137** also as a mixture of four diastereoisomers.

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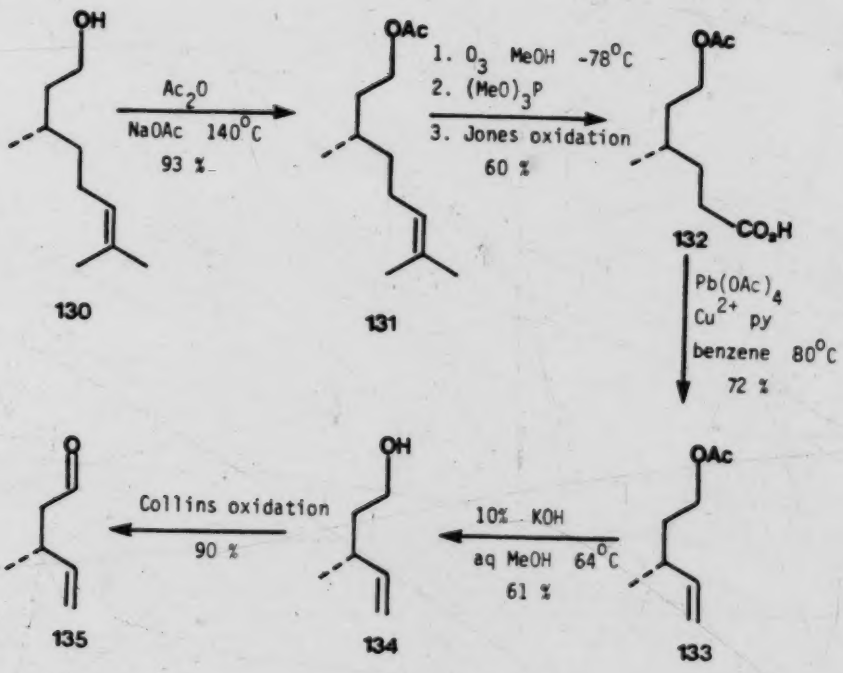
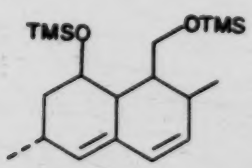
*This work was done by Dr. S. Selvaraj.[67]
Alcohol **134 has been prepared by a similar route.[135]

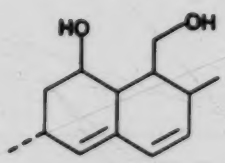
Scheme 37



Desilylation to diol **138** was accomplished (94%) by brief treatment with tetrabutylammonium fluoride.[93]

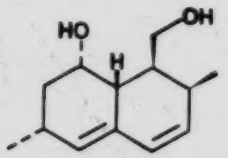


137

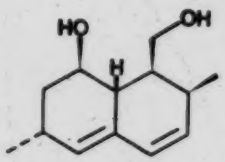


138

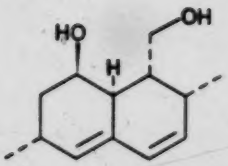
This compound, too, appeared to be a mixture of four diastereoisomers, presumed from the mode of formation to have structures **138a** through **138d**. These are the result of diastereoisomerism from the aldol condensation (with respect to centers C-1 and C-8a) and diastereoisomerism from reacting an optically active aldehyde with a racemic enone (producing diastereoisomers with respect to C-3 and the four other asymmetric centers).



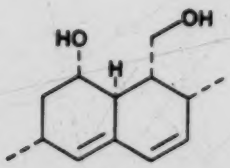
138a



138b



138c



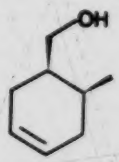
138d

In order to establish whether or not racemization at C-3 occurs during this sequence and in order to prepare the hexahydronaphthalene portions of Mevinolin and Compactin in optically active form, the sequence must be repeated using a chiral enone corresponding to **120**. Work presently underway in our laboratory is directed towards such an enone.

At this stage, we began model studies related to joining the top and bottom portions of Mevinolin and Compactin.

D. Model Studies on the Coupling of the Lactone Unit to the Hexahydronaphthalene Portion of Mevinolin and Compactin

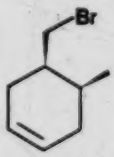
As a suitable model compound for the right hand ring of the bicyclic portion of Mevinolin and Compactin, we chose alcohol **139**.[112] This compound was readily available in large quantity by lithium aluminum hydride reduction of *cis*-ester **108** (99% yield). The latter was an intermediate in our synthesis of enone **120**.



139

Our initial experiments were designed to evaluate the feasibility of the process summarized in Figure 8 as a means of adding the lactone unit to the bicyclic portion.

Alcohol **139** was first converted into bromide **140** (78%) by the action of $(PhO)_3P.Br_2$ in the presence of pyridine.*[113]



140

Attempts to prepare an alkyllithium reagent from bromide **140** were uniformly unsuccessful. No reaction was observed upon treatment with metallic lithium. When lithium-halogen exchange[114] was attempted by adding *tert*-butyllithium (THF, -78°C) to bromide **140**, and the resulting solution was treated either with ethylene oxide or with the lactone synthon **78**, no coupled products were detected.

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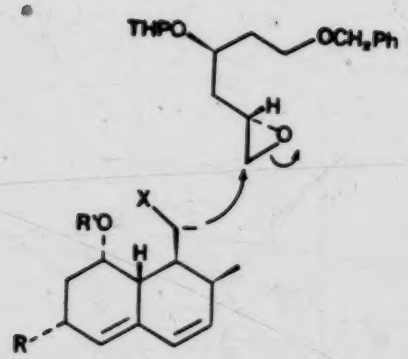
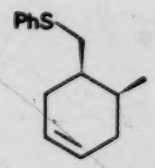
*Treatment of the alcohol with PBr_3 in refluxing ether resulted in an 11% yield of **140**.

Figure 8



Attempts to prepare a Grignard reagent from bromide **140** also failed under a variety of conditions, even when specially activated forms of magnesium were used.[115]

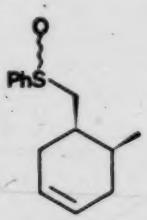
We turned our attention therefore to stabilized anions for the coupling reaction. Alcohol **139** was treated with diphenyl disulfide and tributylphosphine in DMF,[116] and phenyl sulfide **141** was formed in 93% yield.



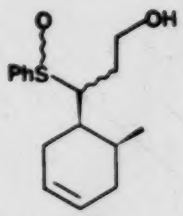
141

This compound could be oxidized to sulfoxide **142** (94%), as a mixture of two diastereoisomers, with aqueous methanolic sodium metaperiodate.[117]

Sulfoxide **142** was deprotonated (n-BuLi, THF) and treated with a large excess of ethylene oxide. Alcohol **143** (as a mixture of four diastereoisomers) was isolated in 55% yield (64% based on recovered starting material).

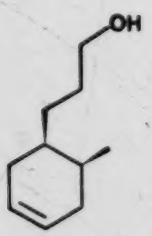


142

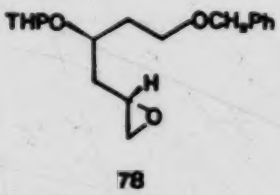


143

Reductive removal of the sulfoxide to afford alcohol **144**, was accomplished (72%) by treatment of **143** with lithium in ethylamine.[111]



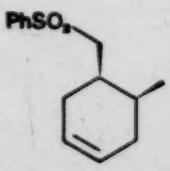
144



78

Unlike this sequence with ethylene oxide, we found that our lactone synthon **78** does not react with the anion derived from sulfoxide **142** and can be recovered unchanged under a variety of conditions.*

Sulphone **145** made from sulfoxide **142** by the action of an excess of aqueous-methanolic sodium metaperiodate, proved to be no more reactive towards epoxide **78** than sulfoxide **142**.*



145

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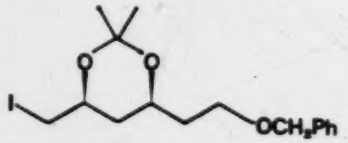
*These experiments were performed by Dr. M. Majewski.[63]

We therefore prepared a modified lactone synthon, iodide **146**, but it too was inert towards the anions derived from sulfoxide **142** and sulphone **145**.*



146

The anions made from **142** and **145** exist in a sterically crowded environment. Possibly, it is this characteristic that renders them unreactive towards epoxide **78** or iodide **146**. In this connection, we did find that a sterically less demanding electrophile such as methyl iodide did alkylate sulfone **145**.* In further work, the anion derived from sulphone **147** was alkylated by iodide **146** as shown in Scheme 38 (which also summarizes the procedure developed in our laboratory,* for elaboration of the β-hydroxy-δ-lactone system).

The less sterically hindered environment of this sulfone anion undoubtedly is a factor in the enhanced reactivity relative to anions derived from **142** and **145**.

We considered that if formation of the C-6',C-7' bond (Figure 9) was not possible, for steric reasons, then formation of the C-5',C-6' bond might be easier because this bond is more distant from regions of steric congestion.

Our overall synthetic strategy readily accommodated the changes needed to implement this idea and a modified approach is shown in Scheme 39.

Preparation of the β-hydroxy-δ-lactone from triol **148** would be accomplished in the fashion previously demonstrated in Scheme 38. The second center of chirality in the lactone portion would be introduced by iodocarbonation of homoallylic alcohol **149**[119] and the C-5',C-6' double bond could then be formed by a Wittig reaction. γ-Hydroxy Wittig reagents such as **150** have been prepared by the action of lithiated phosphorus ylide **151** on epoxides,[120] and a suitable epoxide **74** was actually an intermediate in our preparation of lactone synthon **78** (Scheme 27).

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*These experiments were performed by Dr. M. Majewski.[61]

Scheme 38

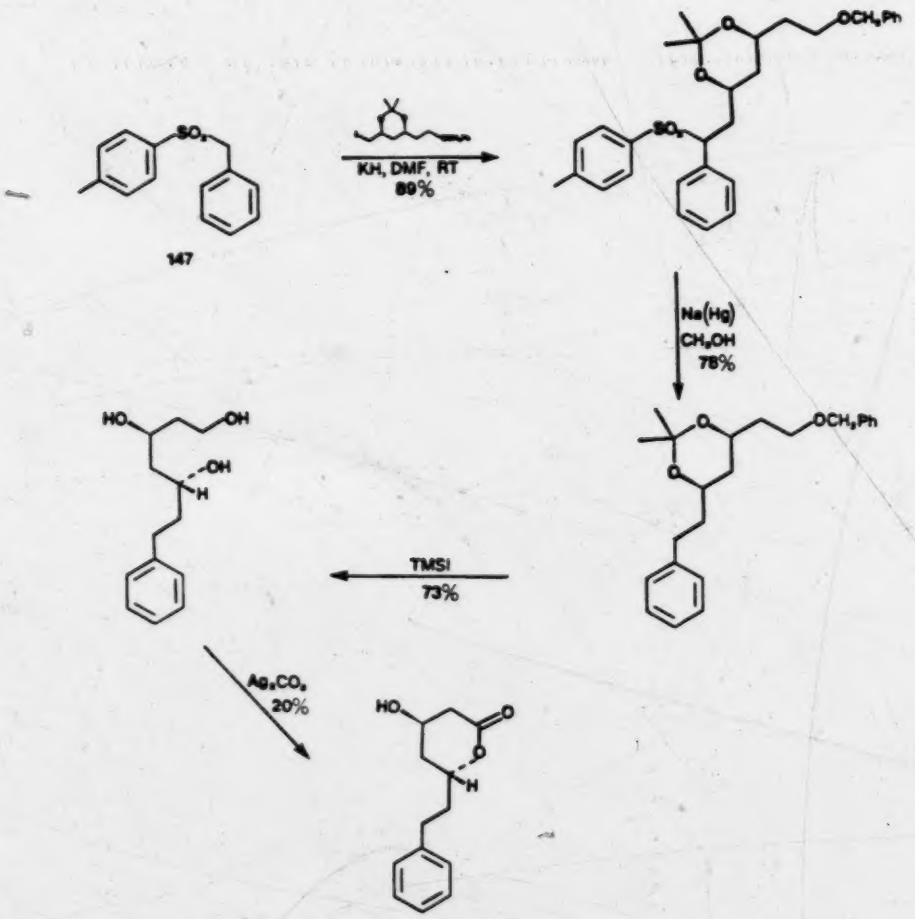
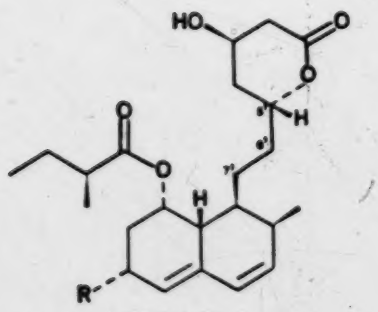
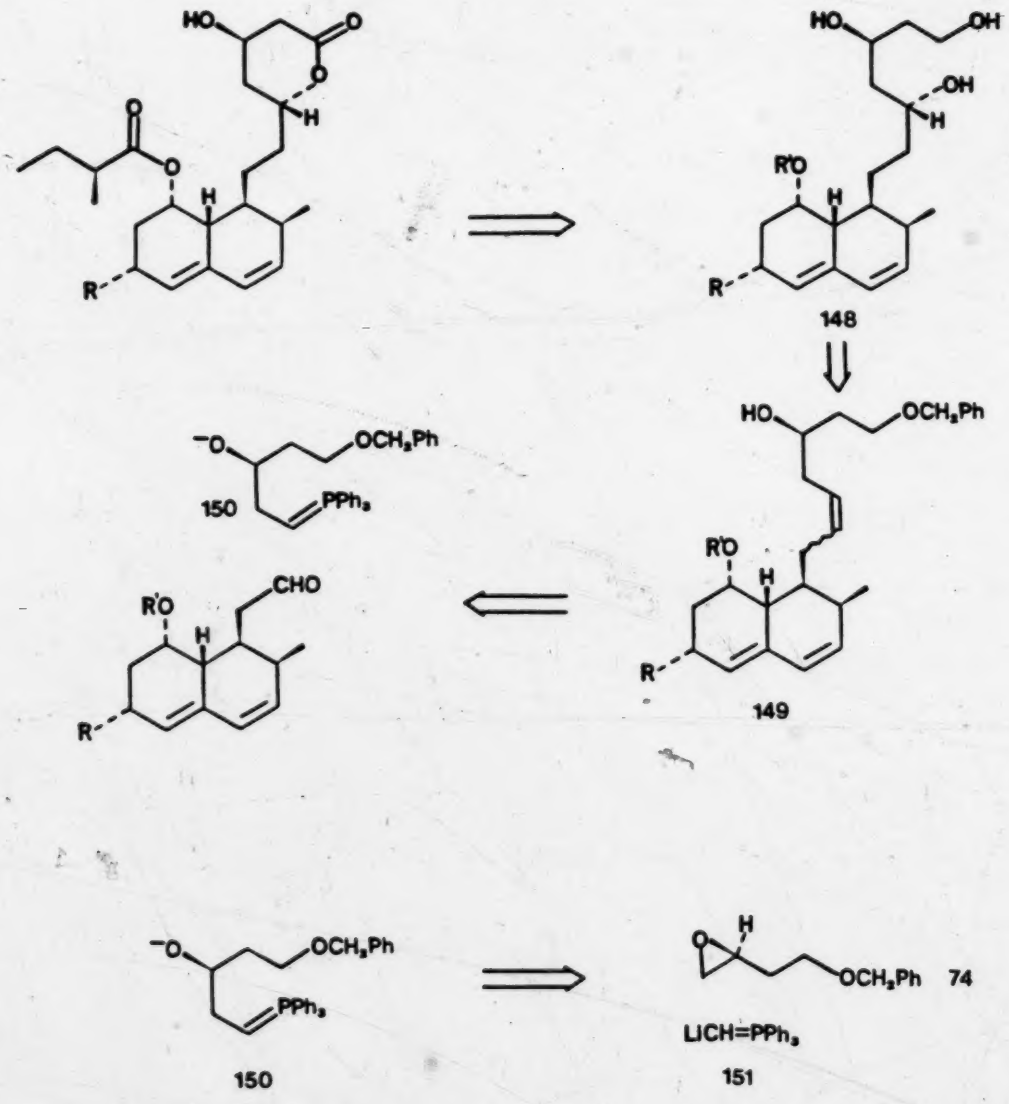


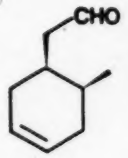
Figure 9



Scheme 39


HO
O
O
H
O
H
R
HO
OH
OH
H
R'O
H
R
148
HO
OCH₂Ph
R'O
H
R
149
⁻O
OCH₂Ph
PPh₃
150
R'O
CHO
H
R
⁻O
OCH₂Ph
PPh₃
150
O
H
OCH₂Ph
74
LiCH=PPh₃
151

To test this method for appending the lactone portion to the bicyclic unit, we chose aldehyde **154** as a suitable model.



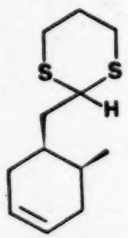
154

This compound was prepared from bromide **140** by reaction with an acyl anion equivalent.*

Treatment of bromide **140** with $Na_2Fe(CO)_4$[122] did provide some aldehyde **154**. However, as has been noted previously,[122] we found it impossible to separate the desired aldehyde **154** from coloured iron containing byproducts.

A modified procedure using a polymer supported $NaFe(CO)_4^-$ reagent[123] was also unsuccessful; the aldehyde was obtained impure and in low yield.

A number of sulfur stabilized anions have been used as nucleophilic acylating agents[121 124] and we examined two of these. When 1,3-dithiane[125] was deprotonated and treated with bromide **140**, the alkylated dithiane **152** was obtained (49%).



152

Attempts to hydrolyse this compound to aldehyde **154** with $HgO\text{-}BF_3.Et_2O$[126] or CuCl-CuO[127] proceeded poorly and so a second sulfur based acyl anion equivalent was examined.

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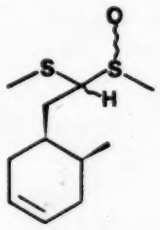
*For a compilation of references to acyl anion equivalents see reference 121.

(Methylsulfinyl)(methylthio)methane[129] was alkylated with bromide **140** to afford compound **153** in 63% yield, as a mixture of four diastereoisomers. This reaction proceeded only when HMPA was added together with bromide **140**.

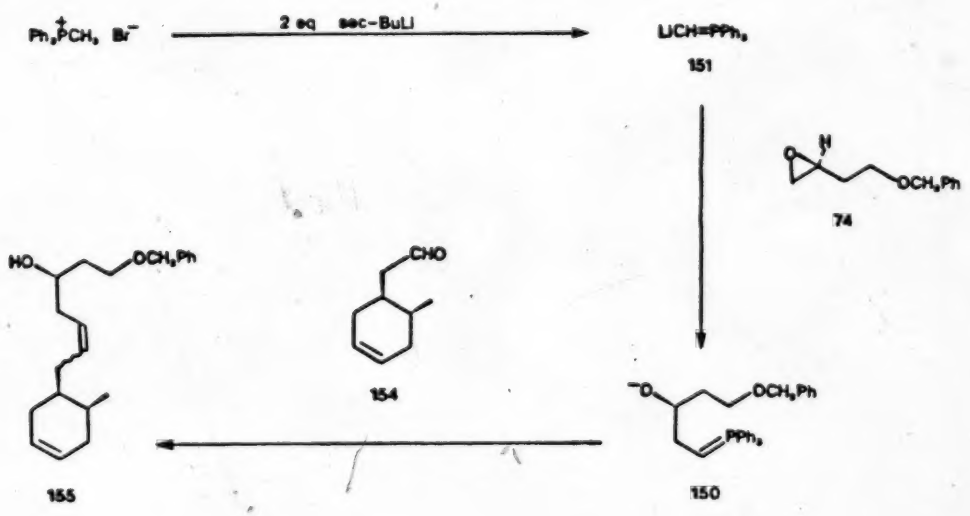


153

Hydrolysis of **153** under the standard conditions ($HClO_4$, THF)[129] produced aldehyde **154** efficiently (81%).

With the model aldehyde in hand, it was possible to examine coupling with epoxide **74** (Scheme 40).

Scheme 40



Lithiated Wittig reagent **151** was generated, and treated with chiral epoxide **74** using the literature procedure.[120] The resulting γ-hydroxy Wittig reagent **150** was treated

with aldehyde **154** and the coupled product **155** was obtained (26%) as a mixture of diastereoisomers. The reaction is expected to produce a *trans* double bond,[129, 130] however, it was unclear from the NMR spectra whether or not this was the case. The yield by this procedure was not optimized since aldehyde **154** represents only a model of the hexahydronaphthalene system. The reaction does however illustrate a possible approach for joining the lower portion of Mevinolin or Compactin to a unit which can, in principle, be elaborated to the β-hydroxy-δ-lactone.

E. Conclusions

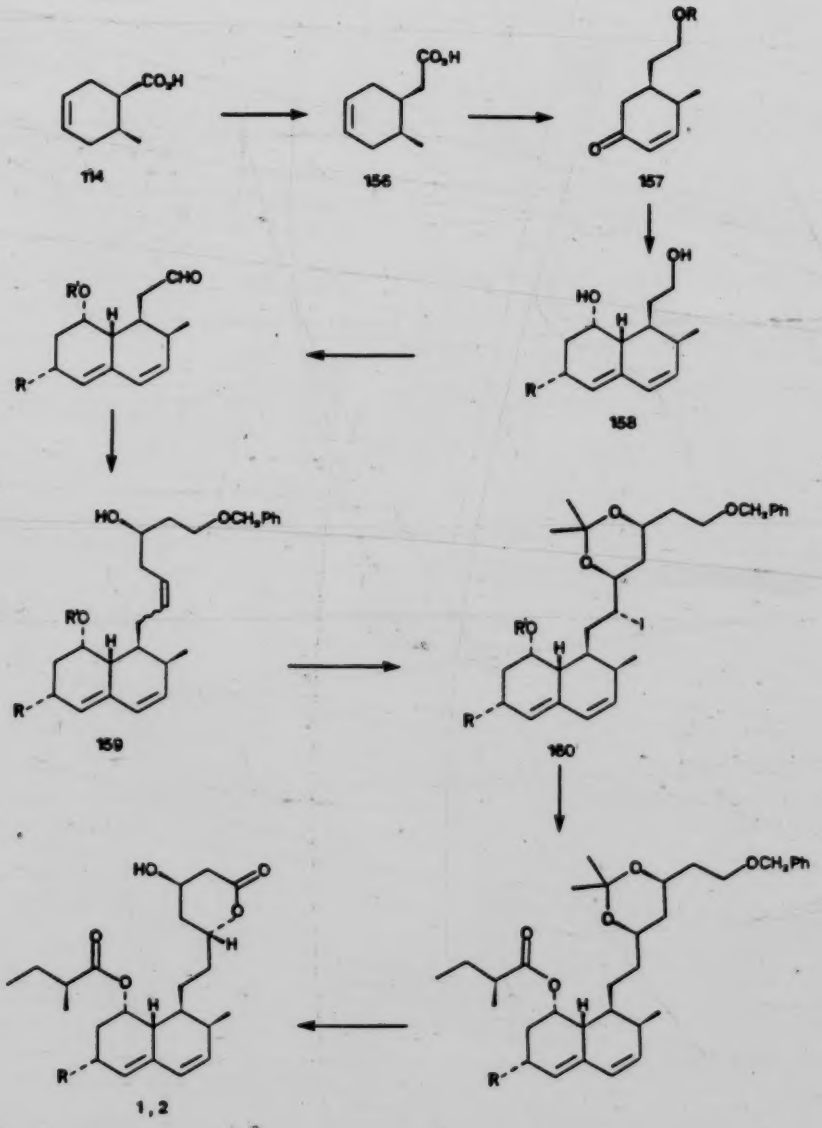
The results described in this thesis demonstrate: a) Our annellation approach is a successful one for preparation of the hexahydronaphthalene portion of Compactin and of a compound possessing the general features of the corresponding portion of Mevinolin. In principle, this route should also be applicable to preparation of analogues of these compounds. b) Our original proposal for attachment of the lactone unit to the bicyclic portion by formation of the C-6',C-7' bond required some modification but the overall plan was sufficiently flexible to accommodate the necessary changes. A route based on formation of the C-5',C-6' bond shows definite promise as a means of coupling the two units.

On the basis of these findings, the following synthetic route (Scheme 41) suggests itself. Further work, to reduce this scheme to practice, will involve: a) Preparation of *cis*-acid **114** in optically active form. b) Conversion of **114** into homologated acid **156** and elaboration of this to enone **157** (by a route analogous to our synthesis of enone **120**). c) Use of our annellation approach to prepare the bicyclic compound **158**. d) Coupling of this unit to chiral epoxide **74** to provide homoallylic alcohol **159**. e) Induction of the second center of chirality in the lactone portion (by iodocarbonation[119]) to afford **160**, and f) Elaboration of this compound to the natural products.

Finally, the flexibility of this strategy is such that the order of some of the steps may be inverted. For example, the lactone unit could be added to the right hand ring of the bicyclic portion before annellation of the left hand ring.

Work along these lines is presently underway in our laboratory.

Scheme 41


CO2H
114
CO2H
156
OR
157
OH
HO
H
R
158
R'O
CHO
H
R
HO
OCH2Ph
R'O
H
R
159
O
O
OCH2Ph
R'O
H
I
R
160
HO
O
O
O
H
O
O
H
R
1, 2
O
O
OCH2Ph
O
O
H
O
R

III. EXPERIMENTAL

General. In addition to the general remarks made in Chapter 1 of this thesis, the following particulars apply. Spinning band distillations were performed using Perkin Elmer model 151 or 251 annular stills. Silica gel for flash chromatography[105] was Merck type 60 (230-400 mesh ASTM). The columns used for vapour phase chromatographic analyses were: 10% Apiezon L, 2% KOH on acid washed Chromosorb W (80-100 mesh), 10% Carbowax 20M on acid washed, dimethylchlorosilane treated Chromosorb W (80-100 mesh), 10% QF1 on acid washed dimethylchlorosilane treated Chromosorb W (80-100 mesh). For ^{13}C NMR spectra, carbon multiplicities, where reported, were determined using the Spin Echo Fourier Transform technique with gated proton decoupling.[131]

Materials. Dry benzene, 1,2-dimethoxyethane (DME), ether, and tetrahydrofuran (THF) were distilled immediately before use from sodium and benzophenone ketyl. Dry diisopropylamine, triethylamine, chloroform, dichloromethane, pyridine, chlorotrimethylsilane and toluene were distilled immediately before use from calcium hydride. Dry hexamethylphosphoric triamide (HMPA) and dimethyl formamide (DMF) were distilled from calcium hydride under reduced pressure (0.1 mm and 15 mm respectively). Dry methanol was distilled immediately before use from magnesium. Deoxygenated water, methanol and ether were obtained by bubbling argon through the solvents for 20 min. Commercial (Aldrich) solutions of *n*-butyllithium in hexane, *sec*-butyllithium in cyclohexane , and *tert*-butyllithium in pentane were titrated before use by the diphenylacetic acid method.[132] Tetrabutylammonium fluoride was purchased as a 1 M solution in THF and was used at the stated concentration. Commercial (Aldrich) $TiCl_3$, Zn-Cu couple (prepared by the literature procedure[81]), and $Na_2Fe(CO)_4$ were stored under argon and transferred to reaction vessels in a glove bag under argon. Dry CrO_3 was stored in a desiccator over Drierite prior to use. The following compounds were prepared by the procedure given in the literature cited: Iodotrimethylsilane,[133] triphenyltin hydride,[100] Lindlar's catalyst ($Pd/CaCO_3$),[84] and anhydrous $MgCl_2$.[115]

4-Pentenal (80).

a) From 4-Pentenol (81). The general procedure of reference 70 was used. Dry CrO_3 (60.00 g, 0.600 mol) was added to a mechanically stirred solution of dry pyridine (97 mL, 95 g, 1.2 mol) in dry CH_2Cl_2 (1.5 L), cooled in ice. The mixture was stirred for 15 min (protection from moisture by a Drierite tube) and then 4-pentenol (**81**) in dry CH_2Cl_2 (*ca.* 10 mL) was added in one portion. The mixture was stirred for a further 15 min at room temperature and the solution was then decanted from the residue which was washed with ether (2 x 200 mL). The combined organic solutions were washed with 5% NaOH (3 x 500 mL), 5% HCl (500 mL), saturated $NaHCO_3$ (500 mL), and saturated NaCl (500 mL). The organic solution was dried and concentrated by distillation through a 20 cm Vigreux column. The residue was distilled (spinning band) to give 4-pentenal (**80**) (3.02 g, 0.0359 mol, 36%) bp 104°C (lit.[72] bp 102-104°C) of greater than 98% purity (VPC, Apiezon, 100°C). Less pure fractions were combined to give more product **80** (1.27 g, 0.0151 mol, 15%) of greater than 80% purity (VPC, Apiezon, 100°C). 4-Pentenal (**80**) had NMR ($CDCl_3$, 100 MHz) δ 9.84 (t, J = 15 Hz, 1H), 5.88 (m, 1H), 5.28-4.93 (m, 2H), 2.73-2.24 (m, 4H), ^{13}C NMR ($CDCl_3$, 22.6 MHz) δ 201.9, 136.5, 115.8, 42.8, 26.2; IR (film) 1725, 1643 cm^{-1}; exact mass, m/e 84.0576 (calcd for C_5H_8O, m/e 84.0570).

b) From 3-Ethenyloxy-1-propene (82). The procedure of reference 71 was used, with some modifications. A mixture of 1-ethenyloxybutane (778 mL, 90%, 602 g, 5.4 mol), 2-propen-1-ol (270 mL, 231 g, 3.98 mol) and mercuric acetate (5 g, 0.02 mol) was distilled carefully through a 60 cm Vigreux column, the distillate with bp less than 65°C being collected. After 6 h, another portion of mercuric acetate (5 g, 0.02 mol) was added, and distillation was continued overnight. The material collected (336 g) was found (VPC; QF1, 50°C) to contain 3-ethenyloxy-1-propene (**82**) (53%) and an impurity (45%) determined (by NMR and VPC) to be 1-ethenyloxybutane. This result is contrary to the reported[71] observation that the product is an azeotrope of (3-ethenyloxy)-1-propene (**82**) and 2-propen-1-ol. The most efficient means of removing the 1-ethenyloxybutane was found to be recycling of the total reaction product: 2-Propen-1-ol (130 mL, 111 g, 1.91 mol) and mercuric acetate (2 g, 0.01mol) were added and distillation was carried out as before. The product (246 g) was found to contain less than 8% of 1-ethenyloxybutane (VPC; QF1, 50°C) and so it was washed with water (100 mL), dried, and redistilled to give

3-ethenyloxy-1-propene (**82**) (209 g, 2.48 mol, 46%) of greater than 95% purity (VPC, QF1, 50°C) which had NMR ($CDCl_3$, 200 MHz) δ 6.27 (dd, J = 14, 7 Hz, 1H), 5.95 (m, 1H), 5.40-5.15 (m, 2H), 4.28-4.10 (m, 3H), 4.05 (dd, J = 6, 2 Hz, 1H); ^{13}C NMR ($CDCl_3$, 50.32 MHz) δ 151.3 (d), 133.2 (d), 117.1 (t), 86.9 (t), 68.8 (t); IR (film) 1635, 1615 cm^{-1}; exact mass, m/e 84.0576 (calcd for C_5H_8O, m/e 84.0575).

4-Pentenal (80). This compound was prepared by the pyrolysis of 3-ethenyloxy-1-propene (**82**) according to the literature procedure[69] except that the yield was usually lower (*ca.* 70%) and the product less pure (*ca.* 70%) (VPC; Apiezon, 100°C) than reported. 4-Pentenal (**80**) of greater than 99% purity (VPC, Apiezon, 100°C) could be obtained from this material by spinning band distillation.

(*R*,R)- and (*R*,S**)-(±)-6-(1-Hydroxy-4-pentenyl)-2-cyclohexen-1-one (83) and (*E*)- and (*Z*)-6-(4-Pentenylidene)-2-cyclohexen-1-one (84).**

a) Using an NH_4Cl Quench. A solution of *n*-butyllithium in hexane (1.48 M, 8.15 mL, 12.1 mmol) was added slowly to a stirred solution of dry diisopropylamine (1.68 mL, 1.21 g, 12.0 mmol) in dry ether (20 mL, cooled to 0°C. The solution was stirred at this temperature for 10 min and was then cooled to -78°C. 2-Cyclohexen-1-one (**79**) (0.964 mL, 0.961 g, 10.0 mol) was added dropwise over *ca.* 10 min. The solution was stirred at this temperature for 30 min and then 4-pentenal (**80**) (1.2 mL, 1.02 g, 12 mmol) was added in one portion, followed after 10 min by saturated NH_4Cl (10 mL). The mixture was warmed to room temperature, the layers were separated, and the aqueous phase was extracted with ether (3 x 15 mL). The combined ether solutions were dried and concentrated. Flash chromatography of the residue over silica gel (15 x 5 cm, 3:1 hexane-ethyl acetate then 1:1 hexane-ethyl acetate) afforded two products. Kugelrohr distillation (130°C, 0.35mm) of the material of higher Rf afforded dehydration product **84** (0.31 g, 1.9 mmol, 19%): NMR ($CDCl_3$, 200 MHz) δ 6.97 (dt, J = 10, 4 Hz, 1H), 6.64 (tm, J = 7.3 Hz, 1H), 6.12 (dt, J = 10, 2 Hz, 1H), 5.78 (m, 1H), 5.13-4.90 (m, 2H), 2.69 (t, J = 6 Hz, 2H), 2.53-2.10 (m, 6H); ^{13}C NMR ($CDCl_3$, 50.32 MHz) showed the presence of two isomers. The major signals in the spectrum appeared at δ 188.3, 149.3, 136.9, 130.7, 115.3, 32.7, 27.1, 24.9, 25.6. Also present were minor signals at δ 137.4, 134.6 and

114.9 which may indicate the presence of a geometrical isomer. IR (film)1675, 1640, 1630, 1615 cm^{-1}; exact mass, m/e 162.1044 (calcd for $C_{11}H_{14}O$, m/e 162.1045). Anal. Calcd for $C_{11}H_{14}O$: C, 81.44; H, 8.70. Found: C, 81.68; H, 8.86. Kugelrohr distillation(140°C, 0.35mm) of the product having lower Rf gave gave aldol **83** (1.00 g, 5.55 mmol, 56%) as an apparently homogeneous (TLC, silica, 3:1 hexane-ethyl acetate) oil: NMR ($CDCl_3$, 400 MHz) showed two diastereoisomers in a ratio of *ca.* 1:1. δ 7.02 (m, 1H), 6.04 (m, 1H), 5.87 (m, 1H), 5.16-4.87 (m, 2H), 4.20 (m, 0.5H), 4.05 (d, J = 3 Hz, 0.5H), 3.92 (m, 0.5H), 2.59 (d, J = 6Hz, 0.5H), 2.56-1.85 (m, 6H), 1.85-1.35 (m, 3H); ^{13}C NMR ($CDCl_3$, 22.6 MHz)* δ 150.9, 150.7, 138.3, 130.2, 129.9, 114.9, 114.7, 71.2, 69.4, 51.6, 33.0, 32.2, 30.5, 29.6, 25.9, 25.2, 22.6; * IR (film) 3450, 1660, 1620 cm^{-1}; exact mass, m/e 180.1146 (calcd for $C_{11}H_{16}O_2$, m/e 180.1150). Anal. Calcd for $C_{11}H_{16}O_2$: C, 73.30; H, 8.95. Found: C, 73.36; H, 9.10.

b) Using an Acetic Acid Quench. A solution of *n*-butyllithium in hexane (1.47 M, 3.74 mL, 5.5 mmol) was added dropwise to a stirred solution of dry diisopropylamine (0.85 mL, 0.61 g, 6.0 mmol) in dry ether (10 mL), cooled to 0°C. The solution was stirred at this temperature for 10 min and then cooled to -78°C. 2-Cyclohexen-1-one (**79**) (0.482 mL, 0.481 g, 5.00 mmol) was added dropwise over *ca.* 10 min. The solution was stirred at this temperature for 1 h, then 4-pentenal (**80**) (0.59 mL, 0.50 g, 6.0 mmol) was added in one portion, followed after 5 s** by glacial acetic acid (0.86 mL, 0.90 g, 15 mmol). The mixture was warmed to room temperature and was then diluted with water (10 mL). The layers were separated and the aqueous phase was extracted with ether (3 x 5 mL). The combined ether solutions were dried and evaporated. Flash chromatography of the residue over silica gel (15 x 2 cm, 17:3 hexane-ethyl acetate then 1:1 hexane-ethyl acetate), and Kugelrohr distillation (130°C, 0.3 mm) gave aldol **83** (577 mg, 3.20 mmol, 64%) as an apparently homogeneous (TLC, silica, 3:1 hexane-ethyl acetate) oil: NMR ($CDCl_3$, 200 MHz) showed two diastereoisomers in a ration of *ca.* 2:1. δ 7.02 (m, 1H), 6.10-5.71 (m, 2H), 5.19-4.90 (m, 2H), 4.20 (m, 0.33H), 4.07 (d, J = 2 Hz, 0.67H), 3.92 (m, 0.67H), 2.71 (d, J = 6 Hz, 0.33H), 2.64-1.90 (m, 6H), 1.90-1.37 (m, 3H). Upon D_2O exchange, the signals at δ 4.07 and 2.71 disappeared. The signal at δ 4.20 simplified to a doublet

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*Not all of the signals for the two diastereoisomers appear in this spectrum.
**Quenching the reaction after 50 s, 5 min or 10 min afforded very similar yields and diastereoisomer ratios.

of triplets, J = 9.6, 3.2 Hz and the signal at δ 3.92 simplified to a doublet of triplets, J = 3.3, 7.5 Hz. Upon irradiation at δ 1.64, the signal at δ 4.20 simplified to a doublet, J = 3 Hz and the signal at δ 3.92 simplified to a doublet, J = 7.3 Hz; ^{13}C NMR ($CDCl_3$, 50.32 MHz) showed two sets of signals which could be separated on the basis of peak heights. The major isomer had, δ 202.6 (s), 150.5 (d), 138.1 (d), 129.3 (d), 114.2 (t), 70.5 (d), 51.3 (d), 32.4 (t), 29.0 (t), 25.3 (t), 24.4 (t). The minor isomer had δ 201.0 (s), 150.3 (d), 137.9 (d), 129.6 (d), 114.3 (t), 68.4 (d), 51.3 (d), 33.0 (t), 30.0 (t), 25.2 (t), 22.0 (t). Some dehydration product **84** was detected (TLC) in the crude reaction mixture, but was not isolated.

(*R,*R**)- and (*R**,*S**)-(±)-6-(1-Acetoxy-4-pentenyl)-2-cyclohexen-1-one (85).** A solution of aldol **83** (219 mg, 1.22 mmol) in dry pyridine (2.0 mL, 1.96 g, 25 mmol) and acetic anhydride (2.0 mL, 2.16 g, 21 mmol) was stirred at room temperature for 4.5 h, diluted with ether (25 mL), and extracted with water (2 x 10 mL), and saturated NaCl (10 mL). The ether solution was dried and evaporated. Flash chromatography of the residue over silica gel (15 x 1 cm, 3:1 hexane-ethyl acetate) and Kugelrohr distillation (100°C, 0.25 mm) gave acetate **85** (2.45 mg, 1.10 mmol, 90%) as an apparently homogeneous (TLC; silica, 3:1 hexane-ethyl acetate) oil. NMR ($CDCl_3$, 100 MHz) δ 7.12-6.82 (m, 1H), 6.13-5.60 (m, 2H), 5.60-5.32 (m, 1H), 5.18-4.86 (m, 2H), 2.88-1.48 (m, 12H containing singlets at δ 2.06 and 2.03); ^{13}C NMR ($CDCl_3$, 50.32 MHz) δ 198.0 (s), 197.9 (s), 170.2 (s), 170.0 (s), 149.7 (d), 149.4 (d), 137.4 (d), 137.3 (d), 129.8 (d), 129.6 (d), 114.8 (t), 114.7 (t), 72.3 (d), 70.7 (d), 49.6 (d), 49.4 (d), 31.3 (t), 30.0 (t), 29.49 (t), 29.45 (t), 25.2 (t), 24.8 (t), 23.2 (t), 22.9 (t), 20.9 (q), 20.7 (q); IR (film) 1735, 1675, 1640, 1620cm^{-1}; exact mass (no M$^+$), m/e 179.1075 (calcd for $C_{11}H_{15}O_2$ (M-C_2H_3O), m/e 179.1072). Anal. Calcd for $C_{13}H_{18}O_3$: C, 70.24; H, 8.16. Found: C, 70.18; H, 8.13.

(*R,*R**)- and (*R**,*S**)- (±)-γ-Acetoxy-2-oxo-3-cyclohexene-1-butanal (86).** Ozone was bubbled through a solution of acetate **85** (305 mg, 1.37 mmol) in dry methanol-CH_2Cl_2 (6 mL of 1:1), cooled to -78°C, until starting material had disappeared (TLC; silica, 1:1 hexane-ethyl acetate). Dimethyl sulfide (0.5 mL, 0.4 g, 7 mmol) was added and the solution was left at room temperature overnight. Evaporation of the solvent and flash

chromatography of the residue over silica gel (15 x 2 cm, 1:1 hexane-ethyl acetate) gave aldehyde **86** (226 mg, 1.01 mmol, 74%) as an apparently homogeneous (TLC; silica, 1:1 hexane-ethyl acetate) oil.* NMR ($CDCl_3$, 100 MHz) δ 9.82 (t, J = 5 Hz, 1H), 7.15-6.87 (m, 1H), 6.09 and 5.99 (2 q, J = 10 Hz, total integration, 1H), 5.61-5.32 (m, 1H), 2.94-1.56 (m, containing singlets at δ 2.06 and 2.04, total integration, 12H); ^{13}C NMR ($CDCl_3$, 22.6 MHz) δ 201.2, 198.1, 170.4, 150.0, 149.8, 129.9, 129.8, 72.3, 70.5, 49.9, 49.7, 40.8, 40.2, 25.4, 25.0, 23.3, 23.0, 21.1, 20.9; IR (film) 1735, 1675, 1620 cm^{-1}; exact mass (no M^+), m/e 164.0831 (calcd for $C_{10}H_{12}O_2$ (M- $C_2H_4O_2$), m/e 164.0837).

Attempted Preparation of (1α, 8aα)- and (1α, 8aβ)- (±)-1, 2, 3, 7, 8, 8a-Hexahydro-1-naphthalenol Acetate (87). The general procedure of reference 81 was used, with some modifications. Dry DME (20 mL) was added to a mixture of $TiCl_3$ (1.14 g, 7.39 mmol) and Zn-Cu couple (1.00 g, 15.4 mmol) and the resulting slurry was heated at reflux for 1 h. A solution of enone aldehyde **86** (78.0 mg, 0.348 mmol) in DME (20 mL) was added by motor driven syringe pump over 10 h, and then the mixture was heated at reflux for an additional 12 h period. The mixture was cooled to room temperature and filtered through a pad of Florisil (2 x 2.5 cm) which was then washed with ether (*ca.* 160 mL). The filtrate was concentrated to afford an oil which appeared (TLC; silica, 3:1 hexane-ethyl acetate) to be a complex mixture of products. IR (film) showed weak -OH (3450 cm^{-1}) and C=O (1740 cm^{-1}) stretches.

Attempted Preparation of (*R,*R**)- and (*R**,*S**)-(±)-6-(1-(Methoxymethoxy)-4-pentenyl)-2-cyclohexen-1-one (88).**

a) A solution of *n*-butyllithium in hexane (1.64 M, 3.05 mL, 5.03 mmol) was added dropwise to a stirred solution of dry diisopropylamine (0.77 mL, 0.56 g, 5.5 mmol) in dry ether (10 mL), cooled to 0°C. The solution was stirred at this temperature for 10 min and then was cooled to -78°C. 2-Cyclohexen-1-one (**79**) (0.482 mL, 0.481 g, 5.00 mmol) was added dropwise over *ca.* 10 min. The solution was stirred at this temperature for 30 min, then 4-pentenal (**80**) (0.49 mL, 0.42 g, 5.0 mmol) was added in one portion, followed after 5 s by chloromethoxymethane (0.75 mL, 0.80 g, 10 mmol), also added in one portion.

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*This compound decomposed at 160°C (0.3 mm), upon attempted distillation.

The solution was stirred at -78°C for 1 h; however, only the aldol product was detected by TLC (silica, 1:1 hexane-ethyl acetate) and so the solution was warmed to room temperature. At this point no aldol product remained (TLC). The solution was poured into water (20 mL) and extracted with ether (3 x 10 mL). The combined ether solutions were dried and concentrated. Flash chromatography of the residue over silica gel (15 x 3 cm, 3:1 hexane-ethyl acetate then 15 x 2 cm, 33:7 hexane-ethyl acetate) and Kugelrohr distillation (115°C, 0.2mm) gave compound **84** (218 mg, 1.34 mmol, 27%), the only major product of the reaction, as an apparently homogeneous (TLC, silica, 1:1 hexane-ethyl acetate oil).

b) Dry triethylamine (0.100 mL, 0.75 g, 0.74 mmol) and chloromethoxymethane (0.056 mL, 0.059 g, 0.74 mmol) were added to a solution of aldol **83** (121 mg, 0.672 mmol) in dry CH_2Cl_2 (3.0 mL). A few mg of 4-(*N*,*N*-dimethylamino)pyridine were added and the solution was stirred at room temperature. After 4 days, the reaction mixture consisted of mostly starting material with the other major component being **84** (TLC, silica, 1:1 hexane-ethyl acetate).

c) The general procedure of reference 82 was used: Dimethoxymethane (*ca.* 1 mL, 11 mmol) and phosphorus pentoxide (0.50 g, 3.5 mmol) were added to a solution of the aldol (38.0 mg, 0.211 mmol) in dry $CHCl_3$ (2.0 mL). After stirring for five days at room temperature some starting material remained and the only major product appeared to be compound **84** (TLC; silica, 1:1 hexane-ethyl acetate).

(*R,*R**)- and (*R**,*S**)-(±)-6-(1-Trimethylsilyloxy-4-pentenyl)-2-cyclohexen-1-one (89).** Dry triethylamine (0.42 mL, 0.30 g, 3.0 mmol) and chlorotrimethylsilane (0.38 mL, 0.33 g, 3.0 mmol) were added to a solution of aldol **83** (451 mg, 2.50 mmol) in dry ether (30 mL). 4-(*N*,*N*-Dimethylamino)pyridine (60 mg, 0.49 mmol) was added and the mixture was stirred overnight at room temperature. The mixture was filtered through a pad of Celite (2 x 2.5 cm) which was then washed with ether (*ca.* 100 mL). Evaporation of the solvent, flash chromatography of the residue over silica gel (15 x 2 cm, 9:1 hexane-ethyl acetate) and Kugelrohr distillation (120°C, 0.35 mm) gave trimethylsilyl aldol **89** (589 mg, 2.33 mmol, 93%) as an apparently homgeneous (TLC; silica, 9:1 hexane-ethyl acetate) oil: NMR ($CDCl_3$, 200 MHz) showed the presence of two diastereoisomers in a ratio of 3.3:1. δ 7.04-6.88

(m, 1H), 6.07-5.70 (m, 2H), 5.11-4.87 (m, 2H), 4.53-4.30 (m, 1H), 2.60-1.30 (m, 9H), 0.13 and 0.07 (2s, total integration 9H, ratio 3.3:1); ^{13}C NMR ($CDCl_3$, 50.32 MHz) showed two sets of signals which could be separated on the basis of peak heights. The major isomer had δ 199.3 (s), 149.6 (d), 138.4 (d), 130.1 (d), 114.2 (t), 70.1 (d), 53.2 (d), 31.9 (t), 30.5 (t), 25.8 (t), 22.0 (t), 0.17 (q). The minor isomer had δ 199.4 (s), 149.9 (d), 138.1 (d), 130.2 (d), 114.4 (t), 69.4 (d), 51.3 (d), 34.7 (t), 30.1 (t), 25.3 (t), 21.4 (t), 0.39 (q). IR (film) 1675, 1642, 1620 cm^{-1}; exact mass, m/e 252.1540 (calcd for $C_{14}H_{24}O_2Si$, m/e 252.1546). Anal. Calcd for $C_{14}H_{24}O_2Si$: C, 66.61; H, 9.58. Found: C, 66.58, H, 9.60.

Ozonolysis of Trimethylsilyl Aldol 89: (*R,*R**)- and (*R**,*S**)-(±)-2-Oxo-γ-trimethylsilyloxy-3-cyclohexene-1-butanal (90) and (*R**,*R**)- and (*R**,*S**)-(±)-2-Oxo-γ-trimethylsilyloxycyclohexanebutanal (91).**

a) Ozonolysis Using a Dimethyl Sulfide Workup. Ozone was bubbled through a solution of trimethylsilyl aldol **89** (504 mg, 2.00 mmol) in 1:1 methanol-dichloromethane (10 mL), cooled to -78°C, until starting material had just disappeared (TLC; silica, 3:1 hexane-ethyl acetate). Dimethyl sulfide (0.50 mL, 0.42 g, 6.8 mmol) was added and the solution was warmed to room temperature. Evaporation of the solvent afforded a very polar (TLC; silica, 1:1 hexane-ethyl acetate) material which was only sparingly soluble in ether. IR (3410 cm^{-1}) showed an alcohol functionality.

b) Ozonolysis in Methanol-Dichloromethane Using a Trimethylphosphite Workup. Ozone was bubbled through a solution of trimethylsilyl aldol **89** (143 mg, 0.568 mmol) in 1:1 methanol-dichloromethane (6 mL) cooled to -78°C, until no starting material remained (TLC; silica, 3:1 hexane-ethyl acetate). Trimethylphosphite (0.25 mL, 0.26 g, 2.1 mmol) was as added at -78°C and the solution was warmed to room temperature. Analysis of the reaction mixture (TLC; silica, 3:1 hexane-ethyl acetate) again showed only very polar material remained.

c) Ozonolysis in Methanol Using a Trimethylphosphite Workup. Ozone was bubbled through a solution of trimethylsilyl aldol **89** (154 mg, 0.608 mmol) in dry methanol (10 mL), cooled to -78°C, until just a trace of starting material remained (TLC; silica, 3:1 hexane-ethyl acetate). Trimethylphosphite (0.100 mL, 0.105 mg, 0.848 mmol) was added

and the solution was left at -78°C for 5 min. The solution was then warmed to room temperature and concentrated. Flash chromatography of the residue over silica gel (15 x 1 cm, 3:1 hexane-ethyl acetate) gave aldehyde **90** (1.16 mg, 0.454 mmol, 74%) as an apparently homogeneous (TLC, silica, 3:1 hexane-ethyl acetate, UV visible spot) oil: NMR ($CDCl_3$, 200 MHz) showed the presence of two diastereoisomers in a ratio of *ca.* 2.1:1. δ 9.80 (t, J = 1.5, 0.68 H), 9.76 (t, J = 1.8 Hz, 0.32H), 7.05-6.91 (m, 1H), 6.08-5.91 (m, 1H), 4.52-4.30 (m, 1H), 2.68-1.60 (m, 9H), 0.12 (s, 6.1H) and 0.07 (s, 2.9H); ^{13}C NMR ($CDCl_3$, 50.32 MHz) showed two sets of signals which could be separated on the basis of peak height. The major isomer had δ 202.1 (d), 199.2 (s), 150.0 (d), 129.9 (d), 69.8 (d), 52.8 (d), 41.0 (t), 25.7 (t), 25.1 (t), 21.8 (t), 0.01 (q). The minor isomer had δ 201.7 (d), 199.0 (s), 150.1 (d), 129.9 (d), 68.7 (d), 51.4 (d), 40.4 (t), 27.8 (t), 25.2 (t), 21.7 (t), 0.17 (q). IR (film) 1740, 1670, 1640 cm^{-1}; exact mass, m/e 254.1333 (calcd for $C_{13}H_{22}O_3Si$, m/e 254.1339). Anal. Calcd for $C_{13}H_{22}O_3Si$: C, 61.38; H, 8.72. Found: C, 61.67; H, 8.65.

d) Ozonolysis Using Workup by Hydrogenation Over Pd/C. Ozone was bubbled through a solution of trimethylsilyl aldol **89** (747 mg, 2.96 mmol) in ethyl acetate (30 mL), cooled to -78°C, until starting material had just disappeared (TLC; silica, 3:1 hexane-ethyl acetate). The solution was warmed to room temperature and 5% palladium on carbon (0.20 g) was added. The mixture was stirred under an atmosphere of hydrogen for 1.5 h and was then filtered through a pad of Celite (2 x 2.5 cm), which was washed with ethyl acetate. Evaporation of the solvent and flash chromatography of the residue over silica gel (15 x 2 cm, 3:1 hexane-ethyl acetate) gave two products: The material of higher Rf keto aldehyde **91** (113 mg, 0.441 mmol, 15%) as an apparently homogeneous (TLC; silica, 3:1 hexane-ethyl acetate, non-UV visible spot) oil: NMR ($CDCl_3$, 100 MHz) δ 9.79 (t, J = 7 Hz, 1H), 4.32-4.06 (m, 1H), 2.66-1.40 (m, 13H), 0.09 (s, 9H); ^{13}C NMR ($CDCl_3$, 100.64 MHz) showed the presence of two diastereoisomers. δ 211.4, 202.6, 202.3, 193.5, 70.0, 69.1, 56.7, 55.7, 42.6, 42.4, 41.0, 40.1, 28.9, 28.3, 27.7, 27.6, 27.5, 27.4, 25.9, 25.0, 24.7, 0.56, 0.37; IR (film) 1715, 1675 cm^{-1}; exact mass, m/e 256.1495 (calcd for $C_{13}H_{24}O_3Si$, m/e 256.1495). The material of lower Rf was enone aldehyde **90** (280 mg, 1.10 mmol, 37%).

e) Ozonolysis Using Workup by Hydrogenation Over Lindlar's Catalyst. Ozone was bubbled through a solution of trimethylsilyl aldol **89** (131 mg, 0.519 mmol) in ethyl acetate (10 mL), cooled to -78°C, until starting material had just disappeared (TLC; silica, 3:1 hexane-ethyl acetate). The solution was warmed to room temperature and Lindlar's catalyst[84] (0.30 g) was added. The mixture was stirred under an atmosphere of hydrogen for 1 h and was then dried and evaporated. Flash chromatography of the residue over silica gel (15 x 1 cm, 3:1 hexane-ethyl acetate) afforded only enone aldehyde **90** (49.3 mg, 0.194 mmol, 37%), as an apparently homogeneous (TLC; silica, 3:1 hexane-ethyl acetate, UV visible spot) oil.

***(R*,R*)-* and *(R*,S*)-*(±)-6-(1-Triethylsilyloxy-4-pentenyl)-2-cyclohexen-1-one (92).** The general procedure of reference 85 was used: Chlorotriethylsilane (1.25 mL, 1.13 g, 7.50 mmol) was added to a solution of aldol **83** (676 mg, 3.75 mmol) in dry pyridine (8.0 mL, 7.8 g, 0.10 mol). The solution was heated at 60°C for 2 h, cooled to room temperature, diluted with ether (50 mL) and extracted with 10% $CuSO_4$ (4 x 20 mL). The combined aqueous extracts were back-extracted with ether (20 mL) and the combined ether solutions were washed with water (20 mL), dried, and concentrated. Flash chromatography of the residue over silica gel (15 x 2 cm, 37:3 hexane-ethyl acetate) and Kugelrohr distillation (125°C, 0.18 mm) gave triethylsilyl aldol **92** (942 mg, 3.20 mmol, 85%) as a clear, colourless, apparently homogeneous (TLC; silica, 3:1 hexane-ethyl acetate) oil: NMR ($CDCl_3$, 100 MHz) δ 7.16-6.86 (m, 1H), 6.19-5.64 (m, 2H), 5.25-4.89 (m, 2H), 4.68-4.38 (m, 1H), 2.74-1.27 (m, 9H), 1.16-0.81 (m, 9H), 0.81-0.42 (m, 6H); ^{13}C NMR ($CDCl_3$, 50.32 MHz) showed two sets of signals which could be separated on the basis of peak height. The major isomer had δ 199.2 (s), 149.6 (d), 138.4 (d), 130.1 (d), 114.1 (t), 70.0 (d), 53.4 (d), 37.1 (t), 30.5 (t), 25.9 (t), 21.8 (t), 6.7 (q), 4.9 (t). The minor isomer had δ 199.3 (s), 149.6 (d), 138.0 (d), 130.3 (d), 114.4 (t), 69.1 (d), 50.6 (d), 34.6 (t), 29.9 (t), 25.2 (t), 20.9 (t), 6.7 (q), 4.9 (t); IR (film) 1675, 1640, 1620 cm^{-1}; exact mass (no M^+), m/e 265.1632 (calcd for $C_{15}H_{25}O_2Si$ ($M-C_2H_5$), m/e 265.1624). Anal. Calcd for $C_{17}H_{30}O_2Si$: C, 69.33; H, 10.27. Found: C, 69.37; H, 10.33.

(*R,*R**)- and (*R**,*S**)- (±)-2-Oxo-γ-triethylsilyloxy-3-cyclohexene-1-butanal (93).**

a) Ozonolysis Using Workup by Hydrogenation Over Lindlar's Catalyst. Ozone was bubbled through a solution of triethylsilyl aldol **92** (72.0 mg, 0.244 mmol) in ethyl acetate (5 mL), cooled to -78°C, until no more starting material remained (TLC; silica, 3:1 hexane-ethyl acetate). The solution was warmed to room temperature, Lindlar's catalyst (0.3 g) was then added, and the mixture was stirred at room temperature under an atmosphere of hydrogen until no more ozonide remained (TLC). The solution was dried, and concentrated. Flash chromatography of the residue over silica gel (15 x 1 cm, 3:1 hexane-ethyl acetate) gave aldehyde **93** (30.6 mg, 0.103 mmol, 42%) as a mixture of two partially resolvable (TLC; silica, 3:1 hexane-ethyl acetate) diastereoisomers: NMR ($CDCl_3$, 100 MHz) δ 9.78 (m, 1H), 7.15-6.79 (m, 1H), 6.04 and 5.94 (m, 1H), 4.63-4.29 (m, 1H), 2.86-2.32 (m, 9H), 1.77-0.26 (m, 6H); IR (film) 1725, 1675, 1640 cm^{-1}; exact mass, m/e 296.1801 (calcd for $C_{16}H_{28}O_3Si$, m/e 296.1808).

b) Ozonolysis Using a Dimethyl Sulfide Workup. Ozone was bubbled through a solution of triethylsilyl aldol **92** (92.5 mg, 0.314 mmol) in dry methanol (7 mL), cooled to -78°C, until no more starting material remained (TLC; silica, 3:1 hexane-ethyl acetate). Dimethyl sulfide (0.25 mL, 0.21 g, 3.4 mmol) was added and, after 30 min, the solution was warmed to room temperature. After 1.5 h at room temperature, reduction was complete (TLC). The solution was concentrated and flash chromatography of the residue over silica gel (15 x 1 cm, 33:7 hexane-ethyl acetate) gave aldehyde **92** (45.2 mg, 0.152 mmol, 49%) as a mixture of two partially resolvable (TLC; silica, 3:1 hexane-ethyl acetate) diastereoisomers.

c) Ozonolysis Using a Trimethylphosphite Workup. Ozone was bubbled through a solution of triethylsilyl aldol **92** (127 mg, 0.431 mmol) in dry methanol (10 mL), cooled to -78°C, until no more starting material remained (TLC; silica, 3:1 hexane-ethyl acetate). Trimethylphosphite (0.12 mL, 0.13 g, 1.0 mmol) was added and after 5 min, the solution was warmed to room temperature. Concentration of the solution and flash chromatography of the residue over silica gel (15 x 1 cm, 33:7 hexane-ethyl acetate) gave aldehyde **93** (67.3 mg, 0.227mmol, 53%) as a partially resolvable (TLC; silica, 3:1 hexane-ethyl acetate) mixture of diastereoisomers.

(*R,*R**)- and (*R**,*S**)-(±)-6-(1-(1, 1-Dimethylethyl)dimethylsilyloxy-4-pentenyl)-2-cyclohexen-1-one (94).** The general procedure of reference 86 was used. *tert*-Butylchlorodimethylsilane (248 mg, 1.65 mmol) was added to a solution of aldol **83** (277 mg, 1.10 mmol) and imidazole (227 mg, 3.33 mmol) in dry DMF (5.0 mL). The mixture was stirred at room temperature for 42 h, poured into water (20 mL) and extracted with ether (4 x 20 mL). The ether solution was dried and concentrated. Flash chromatography of the residue over silica gel (15 x 2 cm, 9:1 hexane-ethyl acetate) and Kugelrohr distillation (120°C, 0.10 mm) gave *tert*-butyldimethylsilyl aldol **94** (186 mg, 0.631 mmol, 57%) as an apparently homogeneous (TLC; silica, 3:1 hexane-ethyl acetate) oil: NMR ($CDCl_3$, 200 MHz) showed the presence of two diastereoisomers in a ratio of *ca.* 2.7:1. δ 6.96 (m, 1H), 6.10-5.70 (m, 2H), 5.14-4.85 (m, 2H), 4.53 (minor isomer) and 4.42 (major isomer) (2 overlapping multiplets, total integration 1H), 2.65-1.20 (m, 10H), 0.96 (s, 6.6H), 0.88 (s, 2.4H), 0.13 (major isomer) and 0.10 (minor isomer) (2 overlapping singlets, total integration 6H); ^{13}C NMR ($CDCl_3$, 50.32 MHz) δ 199.6, 150.0, 149.9, 138.6, 138.1, 130.4, 130.2, 114.6, 114.2, 70.0, 69.2, 53.3, 50.6, 34.6, 32.0, 30.6, 29.9, 26.0, 25.85, 25.76, 25.3, 21.8, 21.0, 17.9,-4.61,-4.65; IR (film) 1675, 1640, 1620 cm^{-1}; exact mass, m/e 294.2015 (calcd for $C_{17}H_{30}O_2Si$, m/e 294.2015). Anal. Calcd for $C_{17}H_{30}O_2Si$: C, 69.33; H, 10.27. Found: C, 69.53; H, 10.25.

2-Methyl-3-buten-2-ol (98). A mixture of 2-methyl-3-butyn-2-ol (125 mL, 109 g, 1.29 mmol), isopentane (175 mL) and Lindlar's catalyst (5 g) were hydrogenated using a Parr Shaker (initial pressure 49 psi) until 1.25 mol of hydrogen had been taken up. The catalyst was removed by filtration and the filtrate was distilled through a 35 cm Vigreux column. After all the solvent had been removed (bp < 30°C), 2-methyl-3-buten-2-ol (**98**) (87.01 g, 1.01 mmol, 78%) was collected as a clear, colourless liquid of greater than 98% purity (VPC; Carbowax, 100°C): bp 92-93.5°C, 700 mm (lit.[90] bp 97-98°C, 760 mm); NMR ($CDCl_3$, 80 MHz) δ 5.95 (dd, J = 17, 10 Hz, 1H), 5.28 (dd, J = 17, 2 Hz, 1H), 4.93 (dd, J = 5, 2 Hz, 1H), 2.07(br s, 1H), 1.28 (s, 6H); IR (film) 3370, 1645 cm^{-1}

5-Methyl-4-hexenal (99). This compound was prepared from alcohol (**98**) using the procedure given in reference 99.

(*R,*R**)- and (*R**,*S**)-(±)-6-(1-Hydroxy-5-ethyl-4-hexenyl)-2-cyclohexen-1-one (100).** A solution of *n*-butyllithium in hexane (1.25 M, 8.0 mL, 10.0 mmol) was added to a stirred solution of dry diisopropylamine (1.54 mL, 1.11 g, 11.0 mmol) in dry ether (20 mL), cooled to 0°C. The solution was stirred at this temperature for 10 min and was then cooled to -78°C. 2-Cyclohexen-1-one (**79**) (0.96 mL, 0.96 g, 10 mmol) was added dropwise over *ca.* 10 min. The solution was stirred at this temperature for 1 h and then aldehyde **99** (1.41 mL, 1.23 g, 11.0 mmol) was added in one portion, followed after 5 min by saturated NH_4Cl (10 mL). The mixture was warmed to room temperature, the layers were separated, and the aqueous phase was extracted with ether (3 x 20 mL). The combined ether solutions were dried and concentrated. Flash chromatography of the residue over silica gel (15 x 5 cm, 3:2 hexane-ethyl acetate) gave aldol **100** (0.90 g, 4.3 mmol, 43%) as an apparently homogeneous (TLC; silica, 1:1 hexane-ethyl acetate) oil: NMR ($CDCl_3$, 200 MHz) showed the presence of two diastereoisomers in a ratio of *ca.* 2.3:1. δ 7.03-6.87 (m, 1H), 5.98 (dm, J = 10 Hz, 1H), 5.09 (tm, J = 6.5 Hz, 1H), 4.15 (m, 0.7H), 3.99 (m, 0.3 H), 3.84 (m, 0.3H), 2.67-1.17 (m, containing singlets at δ 1.69 and 1.63, total integration 15.7H). Upon D_2O exchange, the following changes were noted: the signal at δ 3.99 disappeared. The integration of the multiplet δ 2.67-1.17 changed to 15H. The signal at δ 4.15 sharpened to a doublet of triplets, J = 9.3, 3.3Hz and the signal at δ 3.84 sharpened to a doublet of triplets, J = 3.8, 7.5 Hz; ^{13}C NMR ($CDCl_3$, 50.32 MHz) showed two sets of signals which could be separated on the basis of peak height. The major isomer had δ 201.7 (s), 150.5 (d), 132.0 (s), 130.1 (d), 123.9 (d), 69.3 (d), 51.6 (d), 33.1 (t), 25.7 (t), 25.6 (q), 24.7 (t), 22.4 (t), 17.6 (q). The minor isomer had δ 203.4 (s), 150.7 (d), 131.8 (s), 129.8 (d), 124.1 (d), 71.3 (d), 51.6 (d), 33.7 (t), 25.7 (t), 25.6 (q), 25.0 (t), 23.6 (t), 17.6 (q); IR (film) 3460, 1665 cm^{-1}; exact mass, m/e 208.1464 (calcd for $C_{13}H_{20}O_2$, m/e 208.1464). Anal. Calcd for $C_{13}H_{20}O_2$: C, 74.96; H, 9.68. Found: C, 75.20, H; 9.84.

(*R,*R**)- and (*R**,*S**)-(±)-6-(5-Methyl-1-trimethylsilyloxy-4-hexenyl)-2-cyclohexen-1-one (101).** Dry triethylamine (0.52 mL, 0.38 g, 3.8 mmol) and chlorotrimethylsilane (0.48 mL, 0.41 g, 3.8 mmol) were added to a solution of aldol **100** (712 mg, 3.42 mmol) in dry ether (25 mL). A few mg of 4-(*N*,*N*-dimethylamino)pyridine were added and the mixture

was stirred at room temperature overnight. Additional portions of triethylamine (0.10 mL, 0.07 g, 0.7 mmol) and chlorotrimethylsilane (0.10 mL, 0.090g, 0.8 mmol) were introduced, the mixture was stirred for an additional 4 h at room temperature, and then water (25 mL) was added. The layers were separated and the aqueous phase was extracted with ether (4 x 20 mL). The combined ether solutions were dried and concentrated. Flash chromatography of the residue over silica gel (15 x 3 cm; 21:4 hexane-ethyl acetate) gave trimethylsilyl aldol **101** (707mg, 2.52 mmol, 74%) as a clear, colourless, apparently homogeneous (TLC; silica, 3:1 hexane-ethyl acetate) oil: NMR ($CDCl_3$, 200 MHz) showed the presence of two diastereoisomers in a ratio of *ca.* 2.4:1. δ 7.00-6.83 (m, 1H), 6.04-5.85 (m, 1H), 5.09 (m, 1H), 4.49-4.24 (m, 1H), 2.58-1.19 (m, containing singlets at 1.68 and 1.60, 15H), 0.14 (s, 2.6H), 0.09 (s, 6.4H); ^{13}C NMR ($CDCl_3$, 50.32 MHz) showed two sets of signals which could be separated on the basis of peak height. The major isomer had δ 199.8 (s), 150.0 (d), 131.6 (s), 130.3 (d), 124.0 (d), 69.8 (d), 51.4 (d), 35.7 (t), 25.5 (q), 25.4 (t), 24.6 (t), 21.5 (t), 17.6 (q), 0.36 (q). The minor isomer had δ 199.5 (s), 149.7 (d), 131.3 (s), 130.2 (d), 24.3 (d), 70.6 (d), 53.3 (d), 33.0 (t), 25.8 (t), 25.5 (q), 25.1 (t), 22.2 (t), 17.6 (q), 0.24 (q); IR (film) 1670, 1620 cm^{-1}; exact mass, m/e 280.1859 (calcd for $C_{16}H_{28}O_2Si$, m/e 280.1859). Anal. Calcd for $C_{16}H_{28}O_2Si$: C, 68.52; H, 10.06. Found: C, 68.82; H, 10.14.

Ozonolysis of Trimethylsilyl Aldol 101. Ozone was bubbled through a solution of trimethylsilyl aldol **101** (165 mg, 0.589 mmol) in dry methanol (10 mL), cooled to -78°C, until starting material had just disappeared (TLC; silica, 3:1 hexane-ethyl acetate). Trimethylphosphite (0.100 mL, 0.105 g, 0.848 mmol) was added and, after 5 min, the solution was warmed to room temperature and concentrated. Flash chromatography of the residue over silica gel (15 x 1 cm, 3:1 hexane-ethyl acetate) gave aldehyde **90** (131 mg, 0.515 mmol, 87%) as an apparently homogeneous (TLC; silica, 3:1 hexane-ethyl acetate) oil.*

Attempted Lemieux-Johnson Oxidation of Trimethylsilyl Aldol 89. The general procedure of reference 92 was used: Sodium metaperiodate (381 mg, 1.78 mmol) was

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*Over four experiments, this reaction gave aldehyde **90** in yields ranging from 62% to 87% (average 77%).

added in small portions, over 25 min, to a solution of trimethylsilyl aldol **89** (214 mg, 0.847 mmol) and OsO_4 (16.2 mg, 0.064 mmol) in 1:1 ether-water (6 mL). The solution was stirred at room temperature, following the progress of the reaction by TLC (silica, 3:1 hexane-ethyl acetate). After 24 h, complete decomposition of the starting material **89** had occurred, but none of the desired aldehyde **90** could be detected.

(1α,8aα)- and (1α, 8aβ)-(±)-(1,2,3,7,8,8a-Hexahydro-1-naphthalenyloxy)trimethylsilane (102).

a) The general procedure of reference 81 was used, with some modifications: Dry DME (20 mL) was added to a mixture of $TiCl_3$ (1.47 g, 9.53 mmol) and Zn-Cu couple (1.44 g, 22.0 mmol) and the resulting slurry was heated at reflux for 1 h. A solution of enone aldehyde **90** (derived from aldol **83** which had been prepared by an ammonium chloride quenched aldol condensation) (219 mg, 0.860 mmol) in dry DME (40 mL) was added by motor driven syringe pump over 14 h, and reflux was continued for an additional 24 h. The mixture was then cooled to room temperature and filtered through a pad of Florisil (7 x 2.5 cm, topped with a 1 x 2.5 cm pad of Celite), which was then washed with ether (*ca.* 70 mL) and hexane (*ca.* 70 mL). The filtrate was concentrated and flash chromatography of the residue over silica gel (15 x 1 cm, 19:1 hexane-ethyl acetate) and Kugelrohr distillation (120°C, 0.3 mm) afforded trimethylsilyl ether **102** (106 mg, 0.457 mmol, 55%) as an oil of greater than 99% purity (VPC; QF1, 200°C), partially resolvable (TLC; silica, 19:1 hexane-ethyl acetate) into two diastereoisomers: NMR ($CDCl_3$, 200 MHz) showed two diastereoisomers in a ratio of 1.1:1. δ 6.11-5.96 (m, 1H), 5.80-5.60 (m, 1H), 5.51 (br s, 0.48H), 5.40 (br s, 0.52H), 4.01 (brs, $W_{1/2}$ = 10 Hz, 0.48H), 3.48 (br s, $W_{1/2}$ = 26 Hz, 0.52 H), 2.50-0.95 (m, 9H), 0.16 (s, 4.7H), 0.12 (s, 4.3H); ^{13}C NMR ($CDCl_3$, 50.32 MHz) δ 130.1 (d), 128.9 (d), 127.7 (d), 126.9 (d), 122.9 (d), 122.5 (d), 73.7 (d), 68.7 (d), 43.4 (d), 40.1 (d), 32.2 (t), 30.0 (t), 26.4 (t), 25.9 (t), 25.7 (t), 25.2 (t), 21.0 (t), 0.37 (q), 0.28 (q); IR (film) 1643 cm^{-1}; exact mass, m/e 222.1435 (calcd for $C_{13}H_{22}OSi$, m/e 222.1440). Anal. Calcd for $C_{13}H_{22}OSi$: C, 70.21; H, 9.97. Found: C, 70.22; H, 10.03.

b) Dry DME (20 mL) was added to a mixture of $TiCl_3$ (1.37 g, 8.88 mmol) and Zn-Cu couple (1.33 g, 20.3 mmol) and the resulting slurry as heated at reflux for 1 h. A solution of enone aldehyde **90** (derived from aldol **83** which had been prepared by an acetic acid

quenched aldol condensation) (178 mg, 0.699 mmol) in dry DME (40 mL) was added in one portion and reflux was continued for an additional 24 h. Workup, chromatography and distillation as in part **a)** above afforded trimethylsilyl ether **102** (55.3 mg, 0.249 mmol, 36%) as an oil, partially resolvable (TLC; silica, 19:1 hexane-ethyl acetate) into two diastereoisomers: NMR ($CDCl_3$, 200 MHz) showed the same two isomers as in **a)** above, but in a ratio of 1:3.8. δ 6.04 (m, 1H), 5.77-5.57 (m, 1H), 5.51 (m, 0.79H), 5.40 (m, 0.21H), 4.01 (br s, 0.79 H), 3.48 (m, 0.21H), 2.50-1.48 (m, 9H), 0.15 (s, 1.9H), 0.12 (s, 7.1H); ^{13}C NMR ($CDCl_3$, 50.32 MHz) showed two sets of signals which could be separated on the basis of peak height. The major isomer had δ 134.0 (s), 130.1 (d), 127.0 (d), 122.9 (d), 68.7 (d), 40.1 (d), 30.0 (t), 25.9 (t), 25.7 (t), 21.0 (t), 0.30 (q). The minor isomer had* δ 128.9 (d), 127.8 (d), 122.5 (d), 73.7 (d), 32.2 (t), 25.2 (t).

(1α, 8aα)- (±)-1,2,3,7,8,8a-Hexahydro-1-naphthalenol (103a) and (1α,8aβ)-(±)-1,2,3,7,8,8a-Hexahydro-1-naphthalenol (103b)

a) From Enone Aldehyde 90. The general procedure of reference 81 was used, with some modifictions: Dry DME (20 mL) was added to a mixture of $TiCl_3$ (0.90 g, 5.89 mmol) and Zn-Cu couple (0.91 g, 13.9 mmol) and the resulting slurry was heated at reflux for 1 h. A solution of enone aldehyde **90** (derived from aldol **83** which had been prepared using an acetic acid quenched aldol condensation) (130 mg, 0.509 mmol) in dry DME (20 mL) was added by motor driven syringe pump over 9 h, and reflux was continued for an additional 11 h. The reaction mixture was cooled to room temperature and filtered through a pad of Celite (2 x 2.5 cm), which was then washed with ether (*ca.* 160 mL). The filtrate was concentrated, refiltered as before, and concentrated again. Flash chromatography of the residue over silica gel (15 x 1 cm, 3:1 hexane-ethyl acetate) gave alcohol **103** (56.9 mg, 0.379 mmol, 74%) as an oily solid, partially resolvable (TLC; silica, 3:1 hexane-ethyl acetate) into a mixture of two diastereoisomers: NMR ($CDCl_3$, 100 MHz), showed two diastereoisomers in a ratio of *ca.* 2.3:1. δ 6.10 (br d, J = 10 Hz, 1H), 5.89-5.38 (m, 2H), 4.05 (br s, 0.7H), 3.54 (m, 0.3H), 2.54-1.37 (m, 10H); ^{13}C NMR ($CDCl_3$, 22.6 MHz) showed two sets of signals which could be separated on the basis of peak height. The major isomer had δ 133.4, 129.8, 127.7, 122.6, 68.4, 39.8, 29.1, 25.7,

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*Not all of the signals for the minor isomer were discernible in this spectrum.

25.6, 20.6. The minor isomer had* δ 128.8, 73.0, 43.5, 31.9, 26.2, 25.6, 25.0; IR ($CHCl_3$) 3580, 3450, 1640,1600 cm^{-1}; exact mass, m/e 150.1037 (calcd for $C_{10}H_{14}O$, m/e 150.1045).

b) From Trimethylsilyl Ether 102. A solution of tetrabutylammonium fluoride in THF[101] (1.0 M, 0.5 mL, 0.5 mmol) was added to a solution of trimethylsilyl ether **102** (derived from aldol **83** which had been prepared by an ammonium chloride quenched aldol condensation) (37.7 mg, 0.170 mmol) in THF (2.0 mL) at room temperature. After 10 min, the solution was concentrated and flash chromatography of the residue over silica gel (15 x 0.5 cm, 1:1 hexane-ethyl acetate) afforded alcohol **103** (20.7 mg, 0.138 mmol, 81%) as an oily solid, partially resolvable (TLC, silica, 1:1 hexane-ethyl acetate) into a mixture of two diastereoisomers. NMR ($CDCl_3$, 200 MHz) showed the same two diastereoisomers as from **a)** above, in a ratio of 1:1.5. δ 6.00 (two overlapping doublets, J = 10 Hz, 1H), 5.75-5.58 (m, 1H), 5.49 (m, 0.4H), 5.38 (m, 0.6H), 3.99 (br s, 0.4H), 3.49 (m, 0.60H), 2.44-0.75 (m, 10H). Upon D_2O exchange, the signal at δ 3.99 appeared as a broad singlet ($W_{1/2}$ = 9Hz). The signal at δ 3.49 appeared as a multiplet ($W_{1/2}$ = 35 Hz).

***cis*-(±)-4-Cyclohexene-1,2-dicarboxylic anhydride (112).** This compound was obtained commercially (Aldrich) or was prepared in 80% yield by the Diels-Alder reaction of butadiene sulfone (**111**) and maleic anhydride (**112**) using the procedure given in reference 97.

***cis*-(±)-Δ^4-Tetrahydrophthalide (113).** This compound was prepared in 67% yield by the $LiAlH_4$ reduction of anhydride **112** using the procedure given in reference 98.

***cis*-(±)-6-Methyl-3-cyclohexene-1-carboxylic acid (114).**

a) From Lactone 113. Iodotrimethylsilane (1.24 mL, 1.74 g, 8.68 mmol) was added to a solution of lactone **113** (1.00 g, 7.24 mmol) in dry benzene (20 mL). The solution was stirred at room temperature for 1 h, and then triphenyltin hydride (2.40 mL, 3.30 g, 9.41 mmol) was added. The resulting solution was heated at reflux for 1.5 h, cooled to room temperature and poured into ether (50 mL). The ether solution was extracted with 10% NaOH (4 x 20 mL). The aqueous extracts were back-extracted with

ether (1 x 20 mL), cooled in ice, and acidified with conc. HCl (15 mL). The mixture was extracted with ether (4 x 20 mL). The ether solution was dried and evaporated to give a yellow brown oil. Kugelrohr distillation (130°C, 0.40 mm) gave a yellow oil. This material was taken up in ether (20 mL) and washed with saturated $NaHSO_3$ (20 mL) and with water (10 mL). The combined aqueous extracts were back-extracted with ether (15 mL) and the combined ether solutions were dried, and evaporated. Kugelrohr distillation (130°C, 0.40 mm) gave acid **114**[95] (432 mg, 3.08 mmol, 43%) as a clear, colourless oil of greater than 96% purity (VPC; Apiezon, 175°C): NMR ($CDCl_3$, 100 MHz) δ 11.52 (br s, 1H), 5.66 (s, 2H), 2.88-1.70 (m, 6H), 0.95 (d, J = 6.5 Hz, 3H); ^{13}C NMR ($CDCl_3$, 50.32 MHz) δ 181.7 (s), 125.0 (d), 124.2 (d), 42.5 (d), 32.1 (t), 28.3 (d), 23.3 (t), 15.0 (q); IR (film) 3400-2400, 1705, 1658 cm^{-1}; exact mass, m/e 140.0838 (calcd for $C_9H_{12}O_2$, m/e 140.0829). Anal. Calcd for $C_9H_{12}O_2$: C, 68.55; H, 8.63. Found: C, 68.61; H, 8.74.

b) From Ester 109. A solution of KOH in water (0.5 M, 130 mL, 65 mmol) was added to a solution of ester **108**[96] (5.00 g, 32.4 mmol) in methanol (100 mL) and the resulting solution was stirred at room temperature for 6 h. It was then concentrated *in vacuo* to *ca.* 150 mL, cooled in ice, and acidified to *ca.* pH 2 (pH paper) with HCl (6 M, 10 mL). The mixture was extracted with ether (3 x 100 mL) and the ether solution was dried, and concentrated. Kugelrohr distillation as before gave acid **114**[95] (4.17 g, 2.97 mmol, 92%) as a clear, colourless liquid of greater than 98% purity (VPC; Apiezon, 175°C). To test that no epimerization had occurred during the hydrolysis, one drop of the acid was treated with an excess of ethereal diazomethane. Analysis of the derived methyl ester[96] showed greater than 99.9% *cis*- isomer **108** (VPC; Carbowax, 140°C) was present.

(2-*endo*-4-*exo*)- (±)-4-Bromo-2-methyl-6-oxabicyclo[3.2.1]octan-7-one (115).

a) Direct Bromolactonization of Acid 114. The general procedure of reference 102 was used with some modifications: Acid **114** (1.00 g, 7.3 mmol) was dissolved in aqueous NaOH (0.36 M, 25 mL, 9.0 mmol) and the stirred solution was treated with 2 mL portions of a solution of bromine in CH_2Cl_2 (0.35 M, 22 mL total, 7.8 mmol). The layers were separated and the aqueous phase was extracted with CH_2Cl_2 (2 x 20 mL). The combined organic solutions were washed with saturated $NaHSO_3$ (20 mL) and water (20 mL), dried, and concentrated, to afford a white solid. Flash chromatography of the latter

over silica gel (15 x 3 cm, 17:3 hexane-ethyl acetate) and crystallization from hexane, gave bromolactone **115** (923 mg, 4.21 mmol, 59%) as a white, homogeneous (TLC; silica, 3:1 hexane-ethyl acetate) solid: mp 79-80°C; NMR ($CDCl_3$, 100 MHz) δ 4.80 (br t, J = 4.5 Hz, 1H), 4.41 (br t, J = 4.5 Hz, 1H), 2.81-1.92 (m, 6H), 1.06 (d, J = 6.5 Hz, 3H); ^{13}C NMR ($CDCl_3$, 50.32 MHz) δ 175.9 (s), 78.6 (d), 45.1 (d), 44.2 (d), 36.7 (t), 33.1 (t), 29.2 (d), 18.8 (q); IR (CCl_4) 1795 cm^{-1}; exact mass (no M^+), m/e 139.0754 (calcd for $C_8H_{11}O_2$ (M-Br), m/e 139.0759. Anal. Calcd for $C_8H_{11}O_2Br$: C, 43.86; H, 5.06; O, 14.61. Found: C, 43.73; H, 5.12; O, 14.42.

b) Bromolactonization of the Derived Silver Salt. The general procedure of reference 114 was used with some modifications: acid **114** (5.00 g, 35.7 mmol) was dissolved in methanol (10 mL). The solution was neutralized (pH paper) with 10% NaOH (*ca.* 16 mL) and was then treated (in the dark) with aqueous $AgNO_3$ (1.0M, 45 mL, 45 mmol). The white precipitate was filtered off and washed with 100 mL portions each of water, methanol and acetone (in the dark). The solid was dried under oil pump vacuum overnight (with protection from light) to give the silver salt (8.50 g, 34.4 mmol, 96%) as a greyish white solid. A portion of this silver salt (4.00 g, 16.2 mmol) was suspended in dry DMF (40 mL) and cooled in ice. Bromine (1.6 mL, 5.0 g, 31 mmol) was added dropwise, in the dark. The ice bath was removed and the suspension was stirred for 3 h. The mixture was diluted with ether (to *ca.* 200 mL) and filtered to remove solids. The ether solution was washed with saturated NaCl (3 x 40 mL) and the aqueous washings were back-extracted once with ether (40 mL). The combined ether solutions were dried and concentrated. Flash chromatography of the residue over silica gel (15 x 5 cm, 33:7 hexane-ethyl acetate) and crystallization from hexane gave bromolactone **115** (2.89 g, 13.2 mmol, 81%) as homogeneous (TLC; silica, 3:1 hexane-ethyl acetate) fine white needles.

***endo*-(±)-2-Methyl-6-oxabicyclo[3.2.1]oct-3-en-7-one (116).** Bromolactone **115** (10.00 g, 45.6 mmol) was dissolved in dry toluene (200 mL) and 1,5-diazabicyclo[4.3.0]non-5-ene (16.9 mL, 17.0 g, 137 mmol) was added. The mixture was heated at reflux for 8 h, cooled to room temperature, diluted with ether (500 mL), extracted with 10% HCl (2 x 100 mL), with water (10 mL), and with saturated NaCl (100 mL). The ether solution was dried and concentrated to afford an homogeneous (TLC; silica, 1:1 hexane-ethyl acetate) oil.

The reaction was repeated exactly as above and the combined products were distilled (80°C, 0.2 mm) to give lactone **116** (10.59 g, 76.6 mmol, 84%) as a clear, colourless liquid of greater than 97% purity (VPC; Apiezon, 175°C): NMR ($CDCl_3$, 400 MHz) δ 6.16 (m, 1H), 5.70 (dm, J = 5.1 Hz, 1H), 4.71 (m, 1H), 2.67 (m, 2H), 2.48 (m, 1H), 2.03 (d, J = 11.3 Hz, 1H), 1.11 (d, J = 6.9 Hz, 3H); ^{13}C NMR ($CDCl_3$, 50.32 MHz) δ 176.5 (s), 135.4 (d), 127.5 (d), 72.8 (d), 43.6 (d), 35.8 (t), 33.9 (d), 18.4 (q); IR (film) 1775, 1635 cm^{-1}; exact mass, m/e 138.0681 (calcd for $C_8H_{10}O_2$, m/e 138.0681). Anal. Calcd for $C_8H_{10}O_2$: C, 69.55; H, 7.30. Found: C, 69.66; H, 7.41.

(1α,2α,5α)- (±)-5-Hydroxy-2-methyl-3-cyclohexene-1-methanol (117 (. A solution of lactone **116** (2.00 g, 14.5 mmol) in dry THF (40 mL) was added dropwise to a stirred suspension of $LiAlH_4$ (2.20 g, 58.0 mmol) in THF (50 mL). The mixture was heated at reflux for 4 h, stirred at room temperature for 10 h, and then cooled in ice. Water (8 mL) was added cautiously, followed by 10% NaOH (8 mL) and more water (25 mL). The mixture was filtered and the white precipitate was washed with ethyl acetate. The combined filtrates were dried and concentrated to give an homogeneous (TLC; silica, ethyl acetate) viscous oil. Kugelrohr distillation (170°C, 0.5 mm) then afforded diol **117** (1.89 g, 13.3 mmol, 92%) as a clear, colourless, viscous oil: NMR ($CDCl_3$, 100 MHz) δ 5.71 (m, 2H), 4.28 (br t, J = 6.5 Hz, 1H), 3.63 (d, J = 7 Hz, 2H), 2.58-1.24 (m, 6H), 0.97 (d, J = 6.5 Hz, 3H); ^{13}C NMR ($CDCl_3$, 50.32 MHz). δ 134.9 (d), 129.6 (d), 66.6 (d), 64.1 (t), 37.5 (d), 30.7 (t), 30.7 (d), 14.8 (q); IR (film) 3600-2500, 1655 cm^{-1}; exact mass, m/e 142.0994 (calcd for $C_8H_{14}O_2$, m/e 142.0994). Anal. Calcd for $C_8H_{14}O_2$: C, 67.57; H, 9.92. Found: C, 67.79; H, 9.94.

***cis*-(±)-5-(Hydroxymethyl)-4-methyl-2-cyclohexen-1-one (118) and *exo*- (±)-1-Methyl-6-oxabicyclo[3.2.1]octan-3-one (119)** Acivated MnO_2[104] (6.60 g, 75.9 mmol) was added to a stirred solution of diol **117** (1.0796 g, 7.59 mmol) in dry $CHCl_3$ (50 mL). The mixture was stirred at room temperature for 3 h, * after which time no starting material remained (TLC; silica, ethyl acetate). The mixture was filtered through a pad of Celite (3 x 2.5 cm), which

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*The time required for this reaction to go to completion depended on the particular batch of MnO_2. In general the longer the reaction time, the more of compound **119** was formed and the lower the yield of **118**.

was washed with more $CHCl_3$. The filtrate was concentrated to an oil. Flash chromatography of the oil over silica gel (15 x 3 cm, 1:3 hexane-ethyl acetate) and Kugelrohr distillation (145°C, 0.5 mm) gave enone **118** (906 mg, 6.46 mmol, 85%) as an homogeneous (TLC; silica, ethyl acetate, UV visible spot) oil: NMR ($CDCl_3$, 100 MHz) δ 7.05 (dd, J = 10, 5.5 Hz, 1H), 6.00 (dd, J = 10, 2 Hz, 1H), 3.66 (br d, J = 5 Hz, 2H), 2.96-2.20 (m, 4H), 1.92 (br s, 1H), 1.10 (d, J = 7 Hz, 3H); ^{13}C NMR ($CDCl_3$, 50.32 MHz) δ 199.6 (s), 156.1 (d), 127.6 (d), 62.8 (t), 39.2 (d), 36.0 (t), 30.8 (d), 11.9 (q); IR (film) 3600-3100, 1740, 1625 cm^{-1}; exact mass, m/e 140.0839 (calcd for $C_8H_{12}O_2$, m/e 140.0830). Anal. Calcd for $C_8H_{12}O_2$: C, 68.55; H, 8.63. Found: C, 68.55; H, 8.84. Flash chromatography and Kugelrohr distillation (120°C, 0.35 mm) also afforded ketone **119** (27.5 mg, 0.196 mmol, 3%) as an homogeneous (TLC; silica, ethyl acetate, non-UV visible spot) oil. NMR ($CDCl_3$, 100 MHz) δ 4.28-3.97 (m, 2H), 3.80 (d, J = 9 Hz, 1H), 2.84-2.20 (m, 6H), 1.16 (d, J = 7 Hz, 3H); ^{13}C NMR ($CDCl_3$, 22.6 MHz) δ 209.8, 79.8, 71.8, 49.3, 49.0, 42.7, 40.4, 16.5; IR (film) 1718 cm^{-1}; exact mass, m/e 140.0836 (calcd for $C_8H_{12}O_2$, m/e 140.0838). Anal. Calcd for $C_8H_{12}O_2$: C, 68.55; H, 8.63. Found: C, 68.30; H, 8.65.

***cis*-(±)-4-Methyl-5-(trimethylsilyloxymethyl)-2-cyclohexen-1-one (120).** Freshly distilled triethylamine (3.6 mL, 2.6 g, 26 mmol) and chlorotrimethylsilane (3.3 mL, 2.8 g, 26 mmol) were added to a solution of enone **118** (3.00 g, 21.4 mmol) in dry ether (30 mL). 4- (*N*, *N*-Dimethylamino)pyridine (0.26 g, 2.1 mmol) was added and the mixture was stirred at room temperature for 3 h. Water (100 mL) was added to dissolve the salts, the layers were separated, and the aqueous phase was extracted with ether (2 x 50 mL). The combined ether solutions were dried and concentrated. Flash chromatography of the residue over silica gel (15 x 5 cm, 5:3 hexane-ethyl acetate) and Kugelrohr distillation (120°C, 0.45 mm) gave trimethylsilyl enone **120** (4.48 g, 21.1 mmol, 89%) as a clear, colourless, homogeneous (TLC; silica, 3:1 hexane-ethyl acetate) oil: NMR ($CDCl_3$, 100 MHz) δ 6.92 (dd, J = 10, 5.3 Hz, 1H), 5.90 (dd, J = 10, 1.3 Hz, 1H), 3.51 (m, 2H), 2.86-2.10 (m, 4H), 1.00 (d, J = 7 Hz, 3H), 0.06 (s, 9H); ^{13}C NMR ($CDCl_3$, 50.32 MHz) δ 198.8 (s), 155.3 (d), 128.0 (d), 63.1 (t), 39.3 (d), 36.2 (t), 30.9 (d), 12.9 (q), -0.82 (q); IR (film) 1750, 1630 cm^{-1}; exact mass, m/e 212.1227 (calcd for $C_{11}H_{20}O_2Si$, m/e 212.1232). Anal. Calcd for $C_{11}H_{20}O_2Si$: C, 67.21; H, 9.49. Found: C, 67.26; H, 9.67.

***cis*-(±)-4-Methyl-5-(1,1-dimethylethyl)dimethylsilyloxymethyl-2-cyclohexen-1-one (121).** The general procedure of reference 86 was used: *tert*-Butylchlorodimethylsilane (218 mg, 1.45 mmol) and imidazole (196 mg, 2.88 mmol) were added to a solution of enone **118** (135 mg, 0.963 mmol) in dry DMF (2.0 mL). The mixture was stirred at room temperature for 30 min, after which no starting material could be detected (TLC; silica, 1:1 hexane-ethyl acetate). The mixture was poured into water (10 mL) and extracted with ether (3 x 5 mL). The ether extracts were dried and concentrated. Flash chromatography of the residue over silica gel (15 x 1 cm, 3:1 hexane-ethyl acetate) and Kugelrohr distillation (145°C, 0.35 mm) gave *tert*-butyldimethysilyl ether **121** (141 mg, 0.555 mmol, 58%) as a clear, colourless, homogeneous (TLC; silica, 1:1 hexane-ethyl acetate) oil of greater than 99% purity (VPC; Apiezon, 200°C): NMR ($CDCl_3$, 100 MHz) δ 6.97 (dd, J = 10, 5Hz, 1H), 5.95 (dd, J = 10, 1.5 Hz, 1H), 3.58 (br d, J = 6 Hz, 2H), 2.68 (m, 1H), 2.51-2.14 (m, 3H), 1.06 (d, J = 7 Hz, 3H), 0.87 (s, 9H), 0.03 (s, 6H); ^{13}C NMR ($CDCl_3$, 22.6 MHz) δ 199.4, 155.7, 128.3, 64.0, 39.6, 36.5, 31.3, 25.9, 18.2, 12.4; IR (film) 1680, 1616 cm^{-1}; exact mass (no M^+), m/e 197.0998 (calcd for $C_{10}H_{17}O_2Si$ (M - C_4H_9), m/e 197.0995). Anal. Calcd for $C_{14}H_{26}O_2Si$: C, 66.09; H, 10.30. Found: C, 66.06; H, 10.32.

(4*R,5*R**,6*R**)-(±)-4-Methyl-5-trimethylsilyloxymethyl-6-((*S**)-1-hydroxy-4-pentenyl)-2-cyclohexen-1-one (123a) and (4*R**,5*R**,6*R**)-(±)-4-Methyl-5-trimethylsilyloxymethyl-6-((*R**)-1-hydroxy-4-pentenyl)-2-cyclohexen-1-one (123b)**

a) Using an Acetic Acid Quench A solution of *n*-butyllithium in hexane (1.71 M, 1.3 mL, 2.2 mmol) was added to a stirred solution of dry diisopropylamine (0.34 mL, 0.24 g, 2.4 mmol) in dry ether (10 mL), cooled to 0°C. The solution was stirred at this temperature for 10 min, and then cooled to -78°C. A solution of enone **120** (425 mg, 2.00 mmol) in dry ether (3.0 mL plus 2.0 mL rinse) was added dropwise, over *ca.* 10 min. The solution was stirred at this temperature for 1 h, and then 4-pentenal (**80**) (0.395 mL, 0.336 g, 4.00 mmol) was added in one portion, followed after 15 s, by glacial acetic acid (0.343 mL, 0.360 g, 6.00 mmol). The solution was warmed to room temperature and was then diluted with water (10 mL). The layers were separated and the aqueous phase was extracted with ether (3 x 15 mL). The combined ether solutions were washed with saturated $NaHCO_3$ (20 mL) and saturated NaCl (20 mL), dried, and concentrated. Flash

chromatography of the residue over silica gel (15 x 2 cm, 3:1 hexane-ethyl acetate) gave aldol **123** (520 mg, 175 mmol, 88%) as an oil, partially resolvable (TLC; silica, 3:1 hexane-ethyl acetate) into a mixture of two diastereoisomers. NMR ($CDCl_3$, 200 MHz) showed the two isomers to be in a ratio of 1.6:1. A sample of this mixture (241 mg) was resolved into its component diastereoisomers by flash chromatography over silica gel (15 x 2 cm, 17:3 hexane-ethyl acetate, then 4:1 hexane-ethyl acetate). Mixed fractions were rechromatographed (four chromatographies in all). The diastereoisomer having the higher Rf, **123a** (72.0 mg, 30% recovery, minor isomer) had: NMR ($CDCl_3$, 200 MHz) δ 6.96 (dd, J = 10.1, 5.2 Hz, 1H), 5.93 (dd, J = 10.1, 1.5 Hz, 1H), 5.83 (m, 1H), 5.14-4.93 (m, 2H), 3.78 (m, 1H), 3.70-3.50 (m, containing a singlet at δ 3.58, total integration 3H), 2.87 (m, 1H), 2.76 (dd, J = 10.5, 5.2 Hz, 1H), 2.47-2.02 (m, 3H), 1.67-1.50 (m, 2H), 1.11 (d, J = 7.5 Hz, 3H), 0.14 (s, 9H). Upon D_2O exchange, the following changes were observed. The signal at δ 3.78 simplified to a doublet of triplets, J = 8.3, 5.3 Hz and the signal at δ 3.58 disappeared, leaving between δ 3.70 and 3.50 the AB portion of an ABX system. Upon decoupling the signal at δ 3.78, the signal at δ 2.76 collapsed to a doublet, J = 11 Hz, and the two proton signal at δ 1.67-1.50 simplified somewhat. Upon decoupling the 3 proton doublet at δ 1.11, the signal at δ 2.87 simplified to a broad triplet, J = 4.6 Hz, ^{13}C NMR ($CDCl_3$, 100.64 MHz) δ 202.7, 155.8, 138.4, 128.4, 115.0, 70.8, 61.4, 50.4, 40.9, 32.2, 31.3, 30.3, 13.5,-0.70; IR (film) 3430, 1665 cm^{-1}; exact mass, m/e 296.1816 (calcd for $C_{16}H_{28}O_3Si$, m/e 296.1808). Anal. Calcd for $C_{16}H_{28}O_3Si$: C, 64.82, H, 9.52. Found: C, 64.94; H, 9.57. The diastereoisomer of lower Rf **123b** (128 mg, 53% recovery, major isomer) had: NMR ($CDCl_3$, 200 MHz) δ 6.78 (dd, J = 10.1, 4.1 Hz, 1H), 5.92 (dd, J = 10.1, 1.5 Hz, 1H), 5.85 (m, 1H), 5.13-4.92 (m, 2H), 4.02 (m, 1H), 3.69 (d, J = 6.8 Hz, 2H), 2.78 (m, 1H), 2.72 (d, J = 7.2 Hz, 1H), 2.64 (dd, J = 8, 5.5 Hz, 1H), 2.45-2.05 (m, 3H), 1.88-1.52 (m, 2H), 1.13 (d, J = 7.5 Hz, 3H), 0.12 (s, 9H). Upon D_2O exchange, the doublet at δ 2.72 disappeared and the multiplet at δ 4.02 simplified to a quintet, J = 3.8 Hz. Upon decoupling the signal at δ 4.02, the signal at δ 2.64 collapsed to a doublet, J = 8 Hz. The 2 proton multiplet at δ 1.88-1.52 also simplified somewhat; ^{13}C NMR ($CDCl_3$, 100.64 MHz) δ 200.6, 138.5, 128.4, 114.7, 70.1, 62.1, 52.2, 41.8, 34.7, 31.4, 30.0, 14.9,-0.71; IR (film) 3440, 1660 cm^{-1}; exact mass, m/e 296.1796 (calcd for $C_{16}H_{28}O_3Si$, m/e 296.1807). Anal. Calcd for $C_{16}H_{28}O_3Si$: C, 64.82; H, 9.52.

Found: C, 64.55; H, 9.35.

b) Using an Ammonium Chloride Quench. The reaction was performed exactly as for **a)** above except that the reaction mixture was quenched by addition of saturated aqueous NH_4Cl (10 mL). Workup and chromatography as before gave aldol **123** (504 mg, 1.70 mmol, 85%) as an oil, partially resolvable (TLC; silica, 3:1 hexane-ethyl acetate) into a mixture of diastereoisomers. NMR ($CDCl_3$, 200 MHz) showed that the ratio of **123a** to **123b** was 1:1.6.

c) Using a Boron enolate. A solution of *n*-butyllithium (1.71 M, 1.3 mL, 2.2 mmol) was added dropwise to a stirred solution of dry diisopropylamine (0.34 mL, 0.24 g, 2.4 mmol) in dry ether (10 mL), cooled to 0°C. The solution was stirred at this temperature for 10 min, and was then cooled to -78°C. A solution of enone **120** (425 mg, 2.00 mmol) in dry ether (3.0 mL plus 2.0 mL rinse) was added dropwise, over *ca.* 10 min. The solution was stirred at this temperature for 30 min and then dibutylchloroborane[109] (0.415 mL, 0.353 g, 7.2 mmol) was added dropwise. The solution was stirred for 1 h at -78°C and then 4-pentenal (**80**) (0.395 mL, 0.336 g, 4.00 mmol) was added in one portion. After 1 h at -78°C a solution of anhydrous trimethylamine N-oxide[110] in dry methanol (1.0 M, 7.0 mL, 7.0 mmol) was added. The reaction mixture was warmed to room temperature overnight and was then concentrated. Flash chromatography of the residue over silica gel (15 x 2 cm, 4:1 hexane-ethyl acetate, then 3:1 hexane-ethyl acetate) afforded starting enone **120** (106 mg, 0.497 mmol, 25%) and aldol product (169 mg, 0.570 mmol, 28% (37% based on recovered starting material)). The product appeared to be a mixture of two partially resolvable (TLC; silica, 3:1 hexane-ethyl acetate) diastreoisomers; however, spectroscopic examination showed the material to be a more complex mixture of isomers: NMR ($CDCl_3$, 200 MHz) δ 6.95 (dd, J = 10, 5 Hz, 0.31 H), 6.77 (dm, J = 10 Hz, 0.24 H), 6.55 (br d, J = 10 Hz, 0.16H), 6.00-5.61 (m, 1.3H), 5.13-4.87 (m, 1H), 4.10-3.28 (m, 3H), 2.94-1.46 (m, 7H), 1.46-0.60 (m, 5H), 0.10, 0.09, 0.08, 0.06 and 0.04 (all singlets, total integration 10H).

(4*R,5*R**,6*R**)-(±)-4-Methyl-5-trimethylsilyloxymethyl-6-((*S**)-1-trimethylsilyloxy-4-pentenyl)-2-cyclohexen-1-one (124a) and (4*R**,5*R**,6*R**)-(±)-4-Methyl-5-trimethylxilyl-oxymethyl-6-((*R**)-1- trimethylsilyloxy-4-pentenyl)-2-cyclohexen-1-one (124b).** Dry

trimethylamine (0.675 mL, 0.490 g, 4.84 mmol) and chlorotrimethylsilane (0.615 mL, 0.526 g, 4.84 mmol) were added to a solution of the diastereoisomeric aldols **123** (1.0269 g, 3.46 mmol) in dry ether (30 mL). 4-(*N*,*N*-Dimethylamino)pyridine (66.4 mg, 0.544 mmol) was added and the mixture was stirred at room temperature for 18 h. The reaction mixture was filtered through a pad of Celite (2 x 2.5 cm) which was then washed with ether (*ca.* 100 mL). The filtrate was concentrated to a few mL and refiltered as before. Concentration of the solution, and flash chromatography of the residue over silica gel (15 x 3 cm, 19:1 hexane-ethyl acetate) gave trimethylsilyl ether **124** (1.0677 g, 2.90 mmol, 83%) as an apparently homogeneous (TLC, silica, 3:1 hexane-ethyl acetate) oil: NMR ($CDCl_3$, 200 MHz) showed two diastereoisomers **124a** and **124b** in a ratio of *ca.* 1:2.

(4*R,5*R**,6*R**)-(±)-4-Methyl-5-trimethylsilyloxymethyl-6-((*S**)-1-trimethylsilyloxy-4-pentenyl)-2-cyclohexen-1-one (124a).** Dry triethylamine (0.149 mL, 0.108 g, 1.07 mmol) and chlorotrimethylsilane (0.136 mL, 0.116 g, 1.70 mmol) were added to a solution of the minor aldol diastereoisomer **123a** (227 mg, 0.764 mmol) in dry ether (10 mL). 4-(*N*,*N*-Dimethylamino)pyridine (16.5 mg, 0.135 mmol) was added and the mixture was stirred at room temperature overnight. The mixture was filtered through a pad of Celite (2 x 2.5 cm) which was then washed with ether (*ca.* 100 mL). The filtrate was concentrated and flash chromatography of the residue over silica gel (15 x 2 cm, 19:1 hexane-ethyl acetate) afforded trimethylsilyl ether **124a** (240 mg, 0.651 mmol, 85%) as an homogeneous (TLC, silica, 3:1 hexane-ethyl acetate) oil: NMR ($CDCl_3$, 200 MHz) δ 6.66 (dq, J = 10, 1.6 Hz, 1H), 5.95 (dd, J = 10, 2.8 Hz, 1H), 5.85 (m, 1H, X of ABX), 5.13-4.93 (m, 2H, AB of ABX), 4.25 (dt, J = 4, 6.4 Hz; 1H), 3.75 (dd, J = 10, 5.2 Hz, 1H), 3.51 (dd, J = 9.6, 8.8Hz, 1H), 3.25 (m, 1H), 2.63 (dd, J = 3.8, 2.6 Hz, 1H), 2.47 (m, 1H) 2.25-1.98 (m, 2H), 1.77-1.55 (m, 2H), 1.19 (d, J = 7.6 Hz, 3H), 0.11 (s, 9H), 0.08 (s, 1H); ^{13}C NMR ($CDCl_3$, 50.32 MHz) δ 200.5 (s), 153.8 (d), 137.9 (d), 128.7 (d), 114.5 (t), 73.5 (d), 60.5 (t), 51.6 (d), 40.5 (d), 35.2 (t), 30.5 (d), 29.5 (t), 16.8 (q),-0.14 (q),-0.80 (q); IR (film) 1670, 1640 cm^{-1}; exact mass, m/e 368.2200 (calcd for $C_{19}H_{36}O_3Si_2$, m/e 368.2203). Anal. Calcd for $C_{19}H_{36}O_3Si_2$: C, 61.90; H, 9.84. Found: C, 62.06; H, 9.89.

(4*R,5*R**,6*R**)-(±)-4-Methyl-5-trimethylsilyloxymethyl-6-((*R**)-1-trimethylsilyloxy-4-pentenyl)-2-cyclohexen-1-one (124b).** Dry triethylamine (0.297 mL, 0.726 g, 2.13 mmol) and chlorotrimethylsilane (0.271 mL, 0.232 g, 2.13 mmol) were added to a solution of the major aldol diastereoisomer **123b** (452 mg, 1.52 mmol) in dry ether (20 mL). 4-(*N*,*N*-Dimethylamino)pyridine (28.2 mg, 0.231 mmol) was added and the mixture was stirred at room temperature overnight. The mixture was filtered through a pad of Celite (2 x 2.5 cm) which was then washed with ether (*ca.* 100 mL). The filtrate was concentrated and flash chromatography of the residue over silica gel (15 x 2 cm, 19:1 hexane-ethyl acetate) afforded trimethylsilyl ether **124b** (508 mg, 1.38 mmol, 91%) as an homogneous (TLC: silica, 3:1 hexane-ethyl acetate) oil: NMR ($CDCl_3$, 200 MHz) δ 6.95 (dd, J = 10, 4.8 Hz, 1H), 5.89 (dd, J = 10, 1.4 Hz, 1H), 5.83 (m, 1H, X of ABX system), 5.11-4.90 (m, 2H, AB of ABX system), 4.39 (p, J = 4.4 Hz, 1H), 3.95 (dd, J = 10.8, 6 Hz, 1H), 3.53 (dd, J = 10.8, 8.4 Hz, 1H), 2.93 (m, 1H), 2.56 (dd, J = 8.8, 4.8 Hz, 1H), 2.47 (m, 1H), 2.29-1.92 (m, 2H), 1.72-1.37 (m, 2H), 1.11 (d, J = 7.4 Hz, 3H), 0.13 (s, 18H); ^{13}C NMR ($CDCl_3$, 50.32 MHz) δ 198.8 (s), 154.3 (d), 138.3 (d), 128.3 (d), 114.4 (t), 71.7 (d), 61.3 (t), 51.6 (d), 40.7 (d), 33.0 (t), 30.2 (t), 29.9 (d), 13.8 (q), 0.19 (q), -0.74 (q); IR (film) 1670, 1640, 1623 cm^{-1}; exact mass, m/e 368.2204 (calcd for $C_{19}H_{36}O_3Si_2$, 368.2203). Anal. Calcd for $C_{19}H_{36}O_3Si_2$: C, 61.90; H, 9.84. Found: C, 62.47; H, 9.99.

(1*R,5*R**,6*R**, γS*)-(±)-5-Methyl-6-trimethylsilyloxy-methyl-2-oxo-γ-trimethylsilyloxy-3-cyclohexene-1-butanal (125a) and (1*R**, 5*R**, 6*R**, γR*)-(±)-5-Methyl-6-trimethylsilyloxymethyl-2-oxo-γ-trimethylsilyloxy-3-cyclohexene-1-butanal (125b).**

a) Ozonolysis Using a Trimethylphosphite Workup. Ozone was bubbled through a solution of the diastereoisomeric mixture of trimethylsilyl aldols **124** (203 mg, 0.552 mmol) in dry methanol (10 mL), cooled to -78°C, until starting material had just disappeared (TLC; silica, 9:1 hexane-ethyl acetate). The reaction mixture was fairly clean (one major spot, presumably corresponding to the ozonolysis product). Trimethylphosphite (0.10 mL, 0.105 g, 0.848 mmol) was added and, after 5 min, the solution was warmed to room temperature and concentrated. However, analysis of the crude reaction product at this stage (TLC; silica, 9:1 hexane-ethyl acetate) showed no material which moved from the baseline. Furthermore, the residue was no longer soluble

in ether.

b) Ozonolysis Using a Dimethyl Sulfide Workup. Ozone was bubbled through a solution of the diastereoisomeric mixture of trimethylsilyl aldols **124** (36.8 mg, 0.0998 mmol) in dry methanol (5 mL), cooled to -78°C, until starting material had just disappeared (TLC; silica, 3:1 hexane-ethyl acetate). Again, the reaction mixture was fairly clean (one major spot). Dimethyl sulfide (5 drops,*ca.* 0.25 mL, 0.21 g, 3.4 mmol) was added and the solution was warmed to room temperature. Analysis of the crude reaction mixture at this time, however, (TLC; silica, 3:1 hexane-ethyl acetate) again showed total product decomposition, since no TLC mobile material was detected.

c) Ozonolysis Using Workup by Hydrogenation over Lindlar's Catalyst. Ozone was bubbled through a solution of the diastereoisomeric mixture of trimethylsilyl aldols **124** (34.1 mg, 0.0925 mmol) in dichloromethane (5 mL), cooled to -78°C, until starting material had just disappeared (TLC; silica, 3:1 hexane-ethyl acetate). The solution was warmed to room temperature and concentrated. The residue was dissolved in hexane (5 mL), Lindlar's catalyst (*ca.* 0.2 g) was added, and the mixture was stirred at room temperature under an atmosphere of hydrogen. After 24 h, approximately 50% conversion (TLC) to aldehyde **125** had occurred.

d) Ozonolysis Using a Dimethyl Sulfide Workup. Ozone was bubbled through a solution of the diastereoisomeric mixture of trimethylsilyl aldols **124** (34.3 mg, 0.0930 mmol) in dichloromethane (5 mL), cooled to -78°C, until no more starting material remained (TLC; silica, 3:1 hexane-ethyl acetate). The solution was warmed to room temperature and dimethyl sulfide (0.25 mL, 0.21 g, 3.4 mmol) was added. After stirring for 24 h at room temperature, very little conversion to aldehyde **125** had occurred (TLC).

e) Ozonolysis Using a Borane-Dimethyl Sulfide Workup. Ozone was bubbled through a solution of the diastereoisomeric mixture of trimethylsilyl aldols **124** (74.0 mg, 0.201 mmol) in dichloromethane (7 mL), cooled to -78°C, until no more starting material remained (TLC; silica, 3:1 hexane-ethyl acetate). A solution of $BH_3.(CH_3)_2S$ in THF (1.0 M, 0.25 mL, 0.25 mmol) was added and the solution was warmed to room temperature. No aldehyde **125** could be detected (TLC).

f) Ozonolysis Using a Tributylphosphine Workup. Ozone was bubbled through a solution of the diastereoisomeric mixture of trimethylsilyl aldols **124** (133 mg, 0.360

mmol) in dichloromethane (10 mL), cooled to -78°C, until no more starting material remained (TLC, silica, 3:1 hexane-ethyl acetate). Tributylphosphine (0.100 mL, 0.812 g, 0.401 mmol) was added and the solution was warmed to room temperature. After an overnight period at room temperature, none of the desired aldehyde **125** was detected (TLC).

g) Ozonolysis Using a Triphenylphosphine Workup. Ozone was bubbled through a solution of the diastereoisomeric mixture of trimethylsilyl aldols **124** (482 mg, 1.31 mmol) in dry dichloromethane (30 mL), cooled to -78°C, until the starting material had just disappeared (TLC; silica, 3:1 hexane-ethyl acetate). The solution was warmed to room temperature and triphenylphosphine (690 mg, 2.63 mmol) was added. The solution was stirred at room temperature for *ca.* 22 h and was then concentrated. Flash chromatography of the residue over silica gel (15 x 2 cm, 9:1 hexane-ethyl acetate, then 3:1 hexane-ethyl acetate) gave aldehyde **125** (370 mg, 0.999 mmol, 76%) as an apparently homogeneous (TLC; silica, 3:1 hexane-ethyl acetate) oil: NMR ($CDCl_3$, 200 MHz) showed the presence of the two diastereoisomers **125a** and **125b** in a ratio of 1:1.9.

(1*R,5*R**,6*R**, γS*)(±)-5-Methyl-6-trimethylsilyloxymethyl-2-oxo-γ-trimethylsilyl-oxy-3-cyclohexene-1-butanal (125a)**. Ozone was bubbled through a solution of trimethylsilyl aldol **124a** (derived from the minor aldol diastereoisomer **123a**) (200 mg, 0.542 mmol) in dry dichloromethane (15 mL), cooled to -78°C, until the starting material had just disappeared (TLC; silica, 3:1 hexane-ethyl acetate). The solution was warmed to room temperature, triphenylphosphine (285 mg, 1.08 mmol) was added, and the solution was stirred at room temperature for 8 h. Concentration of the solution and flash chromatography of the residue over silica gel (15 x 2 cm, 9:1 hexane-ethyl acetate, then 3:1 hexane-ethyl acetate) gave aldehyde **125a** (135 mg, 0.365 mmol, 67%) as an homogeneous (TLC; silica, 3:1 hexane-ethyl acetate) oil: NMR ($CDCl_3$, 200 MHz) δ 9.79 (t, J = 1.3 Hz, 1H), 6.65 (dq, J = 10, 1.3 Hz, 1H), 5.93 (dd, J = 10, 2.8 Hz, 1H), 4.25 (q, J = 4.5 Hz, 1H), 3.71 (dd, J = 9.5, 4.5 Hz, 1H), 3.51 (dd, J = 9.5, 8.8 Hz, 1H), 3.13 (m, 1H), 2.66-2.35 (m, 4H), 1.98-1.75 (m, 2H), 1.16 (d, J = 7.5 Hz, 3H), 0.06 and 0.04 (2s, total integration 18H); ^{13}C NMR ($CDCl_3$, 50.32 MHz) δ 201.5 (d), 200.1 (s), 154.0 (d), 128.6 (d), 71.9 (d), 60.6 (t), 51.9 (d), 40.7 (d), 39.6 (t), 30.3 (d), 28.0 (t), 16.6 (q), 0.14 (q),-0.77 (q);

IR (film) 1720, 1665 cm^{-1}; exact mass, m/e 370.1961 (calcd for $C_{18}H_{34}O_4Si_2$, m/e 370.1995). Anal. Calcd for $C_{18}H_{34}O_4Si_2$: C, 58.33; H, 9.25. Found: C, 58.53; H, 9.39.

(1*R*•,5*R*•,6*R*•, γ*R*•)-(±)-5-Methyl-6-trimethylsilyloxymethyl-2-oxo-γ-trimethylsilyloxy-3-cyclohexene-1-butanal (125b). Ozone was bubbled through a solution of trimethylsilyl aldol **124b** (derived from the major aldol diastereoisomer **123b**) (220 mg, 0.597 mmol) in dry dichloromethane (15 mL), cooled to -78°C, until the starting material had just disappeared (TLC, silica, 3:1 hexane-ethyl acetate). The mixture was warmed to room temperature, triphenylphosphine (314 mg, 1.19 mmol) was added and the solution was stirred at room temperature for 8 h. Concentration of the solution and flash chromatography of the residue over silica gel (15 x 2 cm, 9:1 hexane-ethyl acetate, then 3:1 hexane-ethyl acetate) gave aldehyde **125b** (162 mg, 0.437 mmol, 73%) as an homogeneous (TLC; silica, 3:1 hexane-ethyl acetate) oil: NMR ($CDCl_3$, 200 MHz) δ 9.79 (t, J = 1.5 Hz, 1H), 6.87 (dd, J = 10, 4.6 Hz, 1H), 5.90 (dd, J = 10, 2 Hz, 1H), 4.41 (p, J = 4.8 Hz, 1H), 3.92 (dd, J = 10.8, 6.4 Hz, 1H), 3.51 (dd, J = 10.8, 8.4 Hz, 1H), 2.94 (m, 1H), 2.61-2.30 (m, containing at δ 2.58 a doublet of doublets, J = 9.2, 4.8 Hz, total integration 4H), 1.98-1.66 (m, 2H), 1.12 (d, J = 7.2 Hz, 3H), 0.12 (s, 18H), ^{13}C NMR ($CDCl_3$, 50.32 MHz) δ 201.9 (d), 198.7 (s), 154.6 (d), 128.1 (d), 71.1 (d), 61.1 (t), 51.3 (d), 40.8 (d), 40.6 (t), 29.9 (d), 26.0 (t), 13.7 (q), 0.08 (q), -0.76 (q); IR (film) 1715, 1660 cm^{-1}; exact mass, m/e 370.1993 (calcd for $C_{18}H_{34}O_4Si_2$ 370.1995). Anal. Calcd for $C_{18}H_{34}O_4Si_2$: C, 58.33; H, 9.25. Found: C, 58.53; H, 9.41.

(1α, 7α, 8α, 8aα)-(±)-(1,2,3,7,8,8a-Hexahydro-7-methyl-8-trimethylsilyloxymethyl-1-naphthalenyloxy)trimethylsilane (126a) and (1α, 7β, 8β, 8aβ)-(±)-(1,2,3,7,8,8a-Hexahydro-7-methyl-8-trimethylsilyloxymethyl-1-naphthalenyloxy)trimethylsilane (126b). The general procedure of reference 81 was used, with some modifications: Dry DME (20 mL) was added to a mixture of $TiCl_3$ (1.00 g, 6.48 mmol) and Zn-Cu couple (1.06 g, 16.2 mmol) and the resulting slurry was heated at reflux for 1 h. A solution of enone aldehyde **125** (155 mg, 0.417 mmol) in dry DME (40 mL) was added by motor driven syringe pump over 14 h and reflux was continued for an additional 24 h. The mixture was then cooled to room temperature and filtered through a pad of Florisil (6 x 2 cm, covered

by a 1 x 2 cm pad of Celite), which was then washed with ether (*ca.* 140 mL). Concentration of the filtrate and flash chromatography of the residue over silica gel (15 x 1 cm, 49:1 hexane-ethyl acetate) gave bistrimethylsilyl ether **126** (117 mg, 0.346 mmol, 83%) as an apparently homogeneous (TLC, silica, 19:1 hexane-ethyl acetate) oil: NMR ($CDCl_3$, 200 MHz) showed the two diastereoisomers **126a** and **126b** in a-ratio of *ca.* 1:1.4.

(1α, 7α, 8α, 8aα)- (±)- (1,2,3,7,8,8a-Hexahydro-7-methyl-8-trimethylsilyloxymethyl-1-naphthalenyloxy)trimethylsilane (126a). The general procedure of reference 81 was used, with some modifications: Dry DME (20 mL) was added to a mixture of $TiCl_3$ (1.13 g, 7.33 mmol) and Zn-Cu couple (1.11 g, 17.0 mmol) and the resulting slurry was heated at reflux for 1 h. A solution of enone aldehyde **125a** (derived from the minor aldol diastereoisomer **123a**) (130 mg, 0.352 mmol) in dry DME (40 mL) was added by motor driven syringe pump over 14 h and reflux was continued for an additional 24 h. The mixture was then cooled to room temperature and filtered through a pad of Florisil (6 x 2 cm, covered by a 1 x 2 cm pad of Celite), which was then washed with ether (*ca.* 140 mL). Concentration of the filtrate and flash chromatography of the residue over silica gel (15 x 1 cm, 49:1 hexane-ethyl acetate) gave bistrimethylsilyl ether **126a** (92.9 mg, 0.274 mmol, 78%) as an homogeneous (TLC, silica, 19:1 hexane-ethyl acetate) oil: NMR ($CDCl_3$, 200 MHz) δ 5.92 (d, J = 10 Hz, 1H), 5.73 (dd, J = 10, 5.5 Hz, 1H), 5.44 (br s, 1H), 3.97 (dd, J = 11, 5.5 Hz, 1H), 3.75 (m, 1H), 3.57 (t, J = 11 Hz, 1H), 2.66 (m, 1H), 2.17 (m, 3H), 2.03-1.73 (m, 2H), 1.73-1.47 (m, 1H), 0.95 (d, J = 7 Hz, 3H), 0.19 (s, 9H), 0.14 (s, 9H). Upon decoupling the signal at δ 0.95, the signal at δ 2.66 collapsed to a triplet, J = 5 Hz; ^{13}C NMR ($CDCl_3$, 50.32 MHz) δ 136.5 (s), 133.9 (d), 127.7 (d), 122.9 (d), 72.7 (d), 63.1 (t), 45.4 (d), 41.1 (d), 32.8 (t), 30.4 (d), 24.5 (t), 13.8 (q), 1.0 (q), -0.33 (q); IR (film) 1650 cm^{-1}; exact mass, m/e 338.2093 (calcd for $C_{18}H_{34}O_2Si_2$, m/e 338.2097).

(1α, 7β, 8β, 8aβ)- (±)- (1,2,3,7,8,8a-Hexahydro-7-methyl-8-trimethylsilyloxymethyl-1-naphthalenyloxyoxy)trimethylsilane (126b). The general procedure of reference 81 was used, with some modifications: Dry DME (20 mL) was added to a mixture of $TiCl_3$* (0.79 g, 5.12 mmol) and Zn-Cu couple (1.75 g, 26.8 mmol) and the resulting slurry was

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*This reagent may have been of inferior quality.

heated at reflux for 1 h. A solution of enone aldehyde **125b** (derived from the major aldol diastereoisomer **123b**) (172 mg, 0.463 mmol) in dry DME (20 mL) was added by motor driven syringe pump over 20 h and reflux was continued for an additional 24 h. The mixture was then cooled to room temperature and filtered through a pad of Florisil (6 x 2 cm, covered by a 1 x 2 cm pad of Celite), which was then washed with ether (*ca.* 140 mL). Concentration of the filtrate and flash chromatography of the residue over silica gel (15 x 1 cm, 49:1 hexane-ethyl acetate) gave bistrimethylsilyl ether **126b** (59.2 mg, 0.175 mmol, 38%) as an homogeneous (TLC, silica, 3:1 hexane-ethyl acetate) white solid: mp 65-67°C; NMR ($CDCl_3$, 200 MHz) δ 5.95 (d, J = 9.5 Hz, 1H), 5.74 (dd, J = 9.5, 6 Hz, 1H), 5.64 (br s, 1H), 4.10 (m, 1H), 3.91 (dd, J = 9.5, 4 Hz, 1H), 3.49 (t, J = 9.5 Hz, 1H), 2.59 (m, 1H), 2.47-1.77 (m, 5H), 1.77-1.53 (m, 1H), 0.96 (d, J = 7 Hz, 3H), 0.18 (s, 9H), 0.16 (s, 9H). Upon decoupling the signal at δ 0.96, the signal at δ 2.59 collapsed to a triplet, J = 5 Hz; ^{13}C NMR ($CDCl_3$, 50.32 MHz) δ 133.7 (s), 133.1 (d), 128.3 (d), 123.3 (d), 65.7 (d), 61.7 (t), 38.2 (d), 37.0 (d), 30.5 (d), 29.8 (t), 20.7 (t), 14.6 (q), 0.59 (q), -0.46 (q); exact mass, m/e 338.2105 (calcd for $C_{18}H_{34}O_2Si_2$, m/e 338.2097). Anal. Calcd for $C_{18}H_{34}O_2Si_2$: C, 63.84; H, 10.12. Found: C, 63.84; H, 10.04.

(1α,7α,8α,8aα)-(±)-1,2,3,7,8,8a-Hexahydro-7-methyl-8-hydroxymethyl-1-naphthalenol (127a) and (1α,7β,8β,8aβ)- (±)-1,2,3,7,8,8a-Hexahydro-7-methyl-8-hydroxymethyl-1-naphthalenol (127b).

a) From Enone Aldehyde 125. The general procedure of reference 81 was used, with some modifications. Dry DME (20 mL) was added to a mixture of $TiCl_3$ (1.10 g, 7.13 mmol) and Zn-Cu couple (1.15 g, 17.5 mmol) and the resulting slurry was heated at reflux for 1 h. A solution of enone aldehyde **125** (224 mg, 0.604 mmol) in dry DME (40 mL) was added by motor driven syringe pump over 16 h and reflux was continued for an additional 12 h. The mixture was then cooled to room temperature and filtered through a pad of Celite (6 x 2 cm) which was then washed with ether (*ca.* 140 mL). Analysis of the reaction mixture at this stage (TLC; silica, 9:1 hexane-ethyl acetate) showed one major product (high Rf). Upon evaporation of the solvent, however, this initial product disappeared, and was replaced by a partially resolvable (TLC; silica, ethyl acetate) mixture of two polar products. Flash chromatography of this material over silica gel (15 x 2 cm, 1:1 hexane-

ethyl acetate, then pure ethyl acetate) gave diol **127** (85.4 mg, 0.440 mmol, 73%) as an oily solid, partially resolvable (TLC, silica, ethyl acetate) into a mixture of two diastereoisomers. NMR ($CDCl_3$, 400 MHz) showed the presence of diols **127a** and **127b** in a ratio of *ca.* 1.3:1. This mixture was resolved into its component diastereoisomers by flash chroamatography over silica gel (15 x 1 cm, 1:3 hexane-ethyl acetate). Flash chromatography of mixed fractions over silica gel (15 x 1 cm, 1:1 hexane-ethyl acetate; 4 chromatographies in all) then finally preparative TLC (20 x 20 cm) eluting with 1:1 hexane-ethyl acetate. The material of higher Rf, diol **127a** (minor isomer) was an oil which failed to crystallize: NMR ($CDCl_3$, 400 MHz) δ 5.94 (d, J = 9.8 Hz, 1H), 5.66 (dd, J = 9.5, 5.8 Hz, 1H), 5.51 (br s, 1H), 4.11 (br s, 1H), 4.02 (br s, 1H), 3.88-3.71 (m, 3H), 2.33 (m, 2H), 2.24 (m, 2H), 2.01 (dq, J = 11.8, 3.3 Hz, 1H), 1.78-1.63 (m, 2H), 0.94 (d, J = 7 Hz, 3H). Upon D_2O exchange, the following changes were observed. The signals at δ 4.11 and δ 4.02 disappeared and the multiplet between δ 3.88 and δ 3.71 sharpened up somewhat. ^{13}C NMR ($CDCl_3$, 100.64 MHz) δ 135.3 (s), 132.8 (d), 128.0 (d), 124.6 (d); 71.8 (d), 66.7 (s), 45.3 (d), 42.1 (d), 34.9 (d), 32.9 (t), 25.1 (t), 15.4 (q); IR ($CHCl_3$) 3595, 3340, 1645 cm^{-1}; exact mass, m/e 194.1304 (calcd for $C_{12}H_{18}O_2$, m/e 194.1307). Anal. Calcd for $C_{12}H_{18}O_2$: C, 74.19; H, 9.39. Found: C, 74.14; H, 9.51. The material of lower Rf, diol **127b** (major isomer) was a white solid which was crystallized from benzene to give fine white needles: mp 118-119.5°C; NMR ($CDCl_3$, 400 MHz) δ 5.96 (d, J = 9.5 Hz, 1H), 5.68 (dd, J = 9.5, 6.0 Hz, 1H), 5.61 (br d, J = 4.8 Hz, 1H), 4.25 (br s, 1H), 3.84 (dd, J = 10, 8.5 Hz, 1H), 3.72 (br d, J = 10 Hz, 1H), 2.88 (br s, 1H), 2.47 (m, 2H), 2.34 (dm, J = 11 Hz, 2H), 2.14 (dtm, J = 17.7, 5.3 Hz, 1H), 2.00 (m, 2H), 1.73 (m, 1H), 0.88 (d, J = 6.5 Hz, 3H). Upon D_2O exchange, the following changes were observed: The signal at δ 2.88 disappeared, the signal at δ 2.47 sharpened up to a broad sextet, J = 6.5 Hz, and integrated to one proton. The signal at δ 4.25 sharpened up somewhat and the signals at δ 3.84 and δ 3.2 sharpened up to two doublets of doublets with J = 10.5, 8.3 Hz and J = 10.5, 3.3 Hz respectively. ^{13}C NMR ($CDCl_3$, 100.64 MHz) δ 133.6 (s), 132.5 (d), 128.6 (d), 123.9 (d), 65.5 (s), 65.3 (d), 40.5 (d), 38.6 (d), 33.3 (d), 28.6 (t), 22.4 (t), 14.7 (q); IR ($CHCl_3$) 3620, 3580, 3440 cm^{-1}; exact mass, m/e 194.1306 (calcd for $C_{12}H_{18}O_2$, m/e 194.1306). Anal. Calcd for $C_{12}H_{18}O_2$: C, 74.19; H, 9.34. Found: C, 74.11; H, 9.33.

b) From Bistrimethylsilyl Ether 126. A solution of tetrabutylammonium fluoride in THF[93] (1.0 M, 0.3 mL, 0.3 mmol) was added to a solution of bistrimethylsilyl ether **126** (56.0 mg, 0.165 mmol) in THF (2.0 mL) at room temperature. After 10 min, the solution was concentrated and flash chromatography of the residue over silica gel (15 x 1 cm, ethyl acetate) afforded diol **127** (26.8 mg, 0.138 mmol) as an oily solid, partially resolvable (TLC, silica, ethyl acetate) into a mixture of two diastereoisomers. NMR ($CDCl_3$, 200 MHz) showed the presence of diols **127a** and **127b** in a ratio of 1:1.6.

(1α,7α,8α,8aα)-(±)-1,2,3,7,8,8a-Hexahydro-7-methyl-8-hydroxymethyl-1-naphthalenol (127a). A solution of tetrabutylammonium fluoride in THF[93] (1.0 M, 0.35 mL, 0.35 mmol) was added to a solution of bistrimethylsilyl ether **126a** (derived from the minor aldol diastereoisomer **123a**) (46.5 mg, 0.137 mmol) in THF (2.0 mL) at room temperature. After 10 min, the solution was concentrated, and flash chromatography of the residue over silica gel (15 x 1 cm, 1:1 hexene-ethyl acetate, then pure ethyl acetate) gave diol **127a** (22.9 mg, 0.18 mmol, 86%) as an homogeneous (TLC, silica, ethyl acetate) oil which solidified on standing, mp 77-79°C. This compound was identical (TLC, ^1H NMR (200 MHz)) to the higher Rf (minor) component of the diol mixture **127**.

(1α,7β,8β,8aβ)-(±)-1,2,3,7,8,8a-Hexahydro-7-methyl-8-hydroxymethyl-1-naphthalenol (127b). A solution of tetrabutylammonium fluoride in THF[93] (1.0 M, 0.75 mL, 0.75 mmol) was added to a solution of bistrimethylsilyl ether **126b** (derived from the major aldol diastereoisomer **123b**) (105 mg, 0.310 mmol) in THF (5.0 mL) at room temperature. After 10 min, the solution was concentrated, and flash chromatography of the residue over silica gel (15 x 1 cm, 1:1 hexane-ethyl acetate, then pure ethyl acetate) gave diol **127b** (57.3 mg, 0.295 mmol, 95%) as an homogeneous (TLC, silica, ethyl acetate) white solid, which was crystallized from benzene; mp 118-119.5°C. This compound was identical (mp, TLC, ^1H NMR (200 MHz)) to the lower Rf (major) component of the diol mixture **127**.

(4*RRSS*,5*RRSS*,6*RRSS*)-4-Methyl-5-trimethylsilyloxymethyl-6-((1*RSRS*,3*RRRR*)-3-methyl-1-trimethylsilyloxymethyl-4-pentenyl)-2-cyclohexen-1-one (136). A solution of n-butyllithium in hexane (1.48 M, 1.48 mL, 2.19 mmol) was added to a solution of dry

diisopropylamine (0.62 mL, 0.45 g, 4.4 mmol) in dry ether (10 mL), cooled to 0°C. The solution was stirred at this temperature for 10 min, and was then cooled to -78°C. A solution of enone **120** (425 mg, 2.00 mmol) in dry ether (3.0 mL plus 2.0 mL rinse) was added dropwise over *ca.* 20 min. The solution was stirred at this temperature for 1 h, and then aldehyde **135** (253 mg of *ca.* 85% pure material, *ca.* 2.2 mmol) in dry ether (2.0 mL) was added, followed, after 5 min, by saturated NH_4Cl (10 mL). The mixture was warmed to room temperature, the layers were separated, and the aqueous phase was extracted with ether (3 x 20 mL). The combined ether solutions were dried and concentrated. Flash chromatography of the residue over silica gel (15 x 2 cm, 33:7 hexane-ethyl acetate, with rechromatography of impure fractions, 15 x 2 cm, 9:1 hexane-ethyl acetate) gave an aldol product (386 mg, 1.24 mmol, 62%) as a partially resolvable (TLC, silica, 3:1 hexane-ethyl acetate) mixture of diastereoisomers: IR (film) 3410, 1670 cm^{-1}.

This product was dissolved in dry ether (30 mL), and treated with dry diisopropylamine (0.21 mL, 0.15 g, 1.5 mmol) and chlorotrimethylsilane (0.19 mL, 0.16 g, 1.5 mmol). 4-(*N*,*N*-Dimethylamino)pyridine (20 mg, 0.16 mmol) was added and the mixture was stirred at room temperature overnight. The reaction mixture was then filtered through a pad of Celite (2 x 2.5 cm), which was washed with ether (*ca.* 100 mL). The filtrate was concentrated and flash chromatography of the residue over silica gel (15 x 2 cm, 9:1 hexane-ethyl acetate, with rechromatography of impure fractions, 15 x 2 cm, 19:1 hexane-ethyl acetate) afforded trimethylsilyl aldol **136** (382 mg, 0.999 mmol, 81%) as a clear, colourless, apparently homogeneous (TLC, silica, 3:1 hexane-ethyl acetate) oil. Spectroscopic analysis, however, indicated the presence of four diastereoisomers: NMR ($CDCl_3$, 200 MHz) δ 6.90-6.78 (m, 0.55H), 6.68-6.55 (m, 0.45H), 5.89-5.81 (m, 1H), 5.81-5.57 (m, 1H), 5.09-4.84 (m, 2H), 4.50-4.36 (m, 0.55H), 4.36-4.20 (m, 0.45H), 4.04-3.86 (m, 0.45H), 3.78-3.64 (m, 0.55H), 3.56-3.40 (m, 1H), 3.34-3.13 (m, 0.5H), 3.00-2.81 (m, 0.5H), 2.65-2.09 (m, 3H), 1.71-1.38 (m, 1H), 1.38-1.20 (m, 1H), 1.20-0.94 (m, composed of 9 peaks, total integration 6H), 0.12, 0.10, 0.07, 0.06, 0.03, 0.00 (6 s, total integration 18H); ^{13}C NMR ($CDCl_3$, 50.32 MHz) showed 56 resolved signals (64 expected for 4 diastereoisomers). Many of these signals appeared in groups of four; IR (film) 1670, 1640, 1625 cm^{-1}; exact mass, m/e 382.2356 (calcd for $C_{20}H_{38}O_3Si_2$, m/e 382.2359).

(1*RSRS*,3*RRRR*,7*RRSS*,8*RRSS*,8a*RRSS*)- (1,2,3,7,8,8a-Hexahydro-3,7-dimethyl-8-trimethylsilyloxymethyl-1-naphthalenyloxy)trimethylsilane (137). Ozone was bubbled through a solution of trimethylsilyl aldol **136** (320 mg, 0.835 mmol) in dry dichloromethane, cooled to -78°C, until starting material had just disappeared (TLC: silica, 3:1 hexane-ethyl acetate). The solution was warmed to room temperature, triphenylphosphine (439 mg, 1.67 mmol) was added and the solution was stirred at room temperature for 14 h. Concentration of the solution and flash chromatography of the residue over silica gel (15 x 2 cm, 19:1 hexane-ethyl acetate, then 9:1 hexane-ethyl acetate) afforded a clear, colourless, apparently homogeneous (TLC: silica, 3:1 hexane-ethyl acetate) oil (192 mg, 0.500 mmol, 60%).

This compound was converted directly to bistrimethylsilyl ether **137** using the general procedure of reference 81: Dry DME (20 mL) was added to a mixture of $TiCl_3$ (1.14 g, 7.39 mmol) and Zn-Cu couple (1.02 g, 15.6 mmol) and the resulting slurry was heated at reflux for 1 h. A solution of the ozonolysis product (192 mg, 0.500 mmol) in dry DME (20 mL) was added by motor driven syringe pump over 16 h and reflux was continued for an additional 12 h. The mixture was then cooled to room temperature and filtered through a pad of Florisil (10 x 2 cm) which was washed with ether (*ca.* 160 mL). Concentration of the filtrate and flash chromatography of the residue over silica gel (15 x 2 cm, 19:1 hexane-ethyl acetate) gave bistrimethylsilyl ether **137** (118 mg, 0.334 mmol, 67%) as an apparently homogeneous (TLC: silica, 19:1 hexane-ethyl acetate) oil: NMR ($CDCl_3$, 400 MHz) showed the presence of 4 diastereoisomers in a ratio of 1.7:1.2:1:1. δ 5.95 (m, 1H), 5.77 (m, 1H), 5.49 (m, 0.33H), 5.43 (m, 0.21H), 5.39 (br s, 0.21H), 5.27 (br s, 0.25H), 4.09 (m, 0.5H), 4.03-3.72 (m, 1.5H), 3.57 (t, J = 12 Hz, 0.5H), 3.51-3.40 (m, 0.5H), 2.70-2.23 (m, 2H), 2.18-1.60 (m, 4H), 1.13, 1.01, 0.98, 0.97 (d, J = 8 Hz and 0.90 (m, total integration 6 H), 0.15, 0.10, 0.09, 0.08 (s, total integration 18H); ^{13}C NMR ($CDCl_3$, 100.64 MHz) δ 135.5 (s), 135.0 (s), 134.4 (d), 134.1 (d), 133.6 (d), 133.3 (d), 133.0 (s), 131.5 (s), 129.6 (d), 129.4 (d), 129.3 (d), 129.1 (d), 128.7 (d), 128.4 (d), 128.0 (d), 127.8 (d), 72.9 (d), 69.0 (d), 66.6 (d), 66.1 (d), 63.2 (t), 63.1 (t), 61.7 (t), 45.5 (d), 45.3 (d), 42.3 (t), 41.4 (d), 41.0 (d), 39.45 (t), 39.40 (t), 38.2 (d), 37.8 (d), 37.0 (d), 36.6 (d), 36.3 (t), 30.6 (d), 30.5 (d), 30.4 (d), 30.3 (d), 29.5 (d), 28.0 (d), 26.1 (d), 23.6 (q), 21.6 (q), 21.5 (q), 21.4 (q), 14.7 (q), 14.6 (q), 13.81 (q), 13.76 (q), 1.13 (q), 1.08 (q), 0.83 (q), 0.63

(q), -0.30 (q), -0.43 (q); IR (film) 1645 cm^{-1}; exact mass, m/e 352.2250 (calcd for $C_{16}H_{32}O_2Si_2$, m/e 352.2253).

(1*RSRS*, 3*RRRR*, 7*RRSS*, 8*RRSS*,8a*RRSS*)-1,2,3,7,8,8a-Hexahydro-3,7-dimethyl-8-hydroxymethyl-1-naphthalenol (138). A solution of tetrabutylammonium fluoride in THF[91] (1.0 M, 1.0 mL, 1.0 mmol) was added to a solution of bistrimethylsilyl ether **137** (147 mg, 0.663 mmol) in THF (3.0 mL) at room temperature. The solution was concentrated and flash chromatography of the residue over silica gel (15 x 0.5 cm, 1:1 hexane-ethyl acetate) gave diol **138** (38.5 mg, 0.185 mmol, 94%) as an oil which appeared to be a partially resolvable (TLC; silica, 1:1 hexane-ethyl acetate) mixture of diastereoisomers: NMR ($CDCl_3$, 200MHz) δ 6.05-5.89 (m, 1H), 5.80-5.63 (m, 1H), 5.59 (br s, 0.29 H), 5.51 and 5.47 (overlapping multiplets, 0.2H), 5.36 (br s, 0.29H), 4.30 (br s, 1.5H), 3.96-3.62 (m, 2.5H), 3.53, 3.23 and 3.10 (overlapping broad singlets, 1H), 2.72-2.20 (m, 3H), 2.20-1.60 (m, 3H), 1.51-0.09 (m, containing doublets at δ 1.23, 0.95, 0.89, 0.88, J = 7 Hz, total integration 6H). Upon D_2O exchange, the following changes were observed: the signal at δ 4.30 sharpened up to a multiplet and integrated for 0.6H. The signals at δ 3.53, 3.23 and 3.10 disappeared. ^{13}C NMR ($CDCl_3$, 50.32 MHz) showed the presence of four diastereoisomers: δ 134.3, 133.2, 133.1, 133.0, 132.9, 131.7, 130.9, 130.6, 130.2, 130.0, 128.7, 128.6, 128.0, 127.9, 71.3, 67.5, 66.1, 66.0, 65.3, 45.0, 42.3, 41.7, 41.5, 40.5, 40.3, 38.8, 38.61, 38.55, 38.5, 38.2, 37.9, 34.9, 34.8, 33.3, 33.0, 30.8, 30.0, 27.7, 25.7, 22.9, 21.6, 21.4, 20.8, 15.2, 14.7, 14.6, 14.0; IR ($CHCl_3$) 3360, 3420 cm^{-1}; exact mass, m/e 208.1467 (calcd for $C_{13}H_{20}O_2$, m/e 208.1463).

***cis*- (±)-6-Methyl-3-cyclohexene-1-methanol (139).** A solution of ester **108** (4.00 g, 25.9 mmol) in dry THF (5 mL) was added dropwise to a suspension of $LiAlH_4$ (1.00 g, 26.4 mmol) in THF (100 mL). The mixture was heated at reflux for 18 h, and was then cooled in ice. Celite (*ca.* 3 g) was added and the mixture was hydrolysed by careful addition of water (3 mL), 10% NaOH (3 mL), and water (9 mL). The precipitate was filtered off and washed with ether (*ca.* 100 mL). The filtrate was washed with saturated NaCl (50 mL) and the aqueous phase was extracted with ether (2 x 25 mL). The combined ether solutions

were dried and concentrated. Kugelrohr distillation of the residue (150°C, 35 mm (lit.[134] bp 92-92.5°C, 10 mm)) gave alcohol **139** (3.22 g, 25.5 mmol, 98%) as an homogeneous (TLC: silica, 3:1 hexane-ethyl acetate) oil of greater than 99% purity (VPC: QF1, 150°C): NMR ($CDCl_3$, 200 MHz) δ 5.63 (m, 2H), 3.57 (m, 2H), 2.32-1.66 (m, 6H), 1.29 (br s, 1H), 0.91 (d, J = 7Hz, 3H); ^{13}C NMR ($CDCl_3$, 50.32 MHz) δ 125.4 (d), 125.0 (d), 63.9 (t), 39.3 (d), 32.4 (t), 27.4 (d), 25.2 (t), 24.1 (q); IR (film) 3650-3100, 1650 cm^{-1}; exact mass, m/e 126.1043 calcd for $C_9H_{14}O$, m/e 126.1044). Anal. Calcd for $C_9H_{14}O$: C, 76.14; H, 11.18. Found: C, 76.11; H, 11.20.

***cis*-(±)-4- (Bromomethyl)-5-methylcyclohexene (140).**

a) Using $(PhO)_3P.Br_2$. The general procedure of reference 113 was used. Bromine (1.46 mL, 4.56 g, 28.5 mmol) was added dropwise to a vigorously stirred, ice cooled solution of triphenylphosphite (8.97 mL, 10.6 g, 34.2 mmol) in dry ether (50 mL), with protection from moisture (Drierite tube). A solution of alcohol **139** (3.00 g, 23.8 mmol) and pyridine (1.92 mL, 1.88 g, 23.8 mmol) in ether (10 mL) was added and the mixture was stirred at room temperature overnight. The mixture was poured into water, the layers were separated, and the aqueous phase was extracted with ether (2 x 50 mL). The combined ether solutions were dried and concentrated. Flash chromatography of the residue over silica gel (15 x 5 cm, hexane) and Kugelrohr distillation (150°C, 15 mm) gave bromide **140** (3.53 g, 18.7 mmol, 78%) as an homogeneous (TLC: silica, hexane) oil of greater than 96% purity (VPC: QF1, 150°C): NMR ($CDCl_3$, 200 MHz) δ 5.61 (m, 2H), 3.48-3.25 (m, 2H), 2.35-1.68 (m, 6H), 0.90 (d, J = 7 Hz, 3H); ^{13}C NMR ($CDCl_3$, 50.32 MHz) δ 125.4 (d), 124.6 (d), 39.8 (d), 36.3 (t), 32.3 (t), 29.4 (d), 27.4 (t), 14.0 (q); IR (film) 1645 cm^{-1}; exact mass, m/e 190.0181 (calcd for $C_9H_{13}{}^{81}Br$, m/e 190.0182), m/e 188.0195 (calcd for $C_9H_{13}{}^{79}Br$, m/e 188.0201). Anal. Calcd for $C_9H_{13}Br$: C, 50.81; H, 6.93. Found: C, 51.07; H, 6.96.

b) Using Phosphorus Tribromide. Phosphorus tribromide (1.9 mL, 5.5 g, 20 mmol) was added dropwise to a stirred solution of alcohol **139** (2.50 g, 19.8 mmol) in dry ether (30 mL) with protection from moisture (Drierite tube). The mixture was then heated at reflux for 4 h, cooled to room temperature, and poured onto an ice-water mixture (*ca.* 200 mL). The mixture was extracted with ether (3 x 10 mL) and the combined ether

extracts were washed with 10 mL each of saturated $NaHCO_3$, water, and saturated NaCl. The organic solution was dried and concentrated. Kugelrohr distillation of the residue (150°C, 15 mm) gave bromide **140** (0.40 g, 2.1 mmol, 11%) as an oil of *ca.* 85% purity (VPC; QF1, 150°C). The IR spectrum (film) showed a weak -OH stretch (3450 cm^{-1}).

Attempted Preparation of an Alkyllithium Reagent from Bromide 140.

a) By Reaction with Lithium Metal. A solution of bromide **140** (351 mg, 1.86 mmol) in dry ether (5.0 mL plus 2.0 mL rinse) was added to lithium dispersion in oil (30% Li, 47.3 mg, 2.04 mmol) and the mixture was heated at reflux for 2 h. A solution of epoxide **78** (121 mg, 0.394 mmol) and HMPA (873 mg, 4.87 mmol) in dry ether (1.0 mL plus 1.0 mL rinse) was added and reflux was continued for 18 h. At this time, analysis of the reaction mixture (TLC; silica, 3:1 hexane-ethyl acetate) showed bromide **140** and epoxide **78** to be the only major components present.

b) By Lithium-Halogen Exchange.[114] A solution of *tert*-butyllithium in pentane (1.96 M, 0.27 mL, 0.53 mmol) was added dropwise to a stirred solution of bromide **140** (50.0 mg, 0.264 mmol) in dry THF (3.0 mL), cooled to -78°C. After 10 min, epoxide **78** (80.3 mg, 0.262 mmol) in dry THF (1.0 mL plus 1.0 mL rinse) was added and the solution was warmed to room temperature. No reaction was observed (TLC; silica, 3:1 hexane-ethyl acetate) and so boron trifluoride etherate (0.032 mL, 0.037 g, 0.026 mmol) was added. After 3 h at room temperature no coupled products could be detected (NMR). Similar observations were made when ethylene oxide was used instead of epoxide **78**.

Attempted Preparation of a Grignard Reagent from Bromide 140. A mixture of anhydrous $MgCl_2$[115] (222 mg, 2.11 mmol) and potassium metal (163 mg, 4.18 mmol) in dry THF (5.0 mL) was heated at reflux for 3 h. Bromide **140** (54.3 mg, 0.287 mmol) in dry THF (1.0 mL plus 1.0 mL rinse) was added and reflux was continued for 2 h. No starting bromide was detected (TLC; silica, 3:1 hexane-ethyl acetate) and so benzaldehyde (33.4 mg, 0.315 mmol) in THF (1.0 mL plus 1.0 mL rinse) was added and reflux was continued for 10 min. None of the desired coupled product was present (TLC comparison with an authentic sample).

cis-(±)-[(6-Methyl-3-cyclohexen-1-ylmethyl)thio]benzene (141). The general procedure of reference 116 was used. Diphenyl disulfide (1.90 g, 8.70 mmol) and tri-*n*-butylphosphine (3.90 mL, 3.20 g, 15.8 mmol) were added to a solution of alcohol **139** (1.00 g, 7.92 mmol) in dry DMF (25 mL). The mixture was stirred at room temperature for 24 h, and was then diluted with ether (250 mL) and extracted with 10% NaOH (3 x 100 mL). The aqueous extracts were back-extracted with ether (100 mL) and the combined ether solutions were dried and concentrated. Flash chromatography of the residue over silica gel (15 x 5 cm, hexane) and Kugelrohr distillation (130°C, 0.5 mm) gave sulfide **141** (1.61 g, 7.37 mmol, 93%) as a clear, colourless, homogenous (TLC; silica, hexane) oil of greater than 98% purity (VPC; QF1, 200°C): NMR ($CDCl_3$, 200 MHz) δ 7.37-7.10 (m, 5H), 5.60 (s, 2H), 2.95 (dd, J = 13, 6 Hz, 1H), 2.78 (dd, J = 13, 8 Hz, 1H), 2.28-1.68 (m, 6H), 0.91 (d, J = 7 Hz, 3H); ^{13}C NMR ($CDCl_3$, 22.6 MHz) δ 137.3, 128.9, 128.8, 125.6, 36.6, 35.8, 32.3, 29.9, 28.3, 14.7; IR (film) 1650 cm^{-1}; exact mass, m/e 218.1126 (calcd for $C_{14}H_{18}S$, m/e 218.1130). Anal. Calcd for $C_{14}H_{18}S$: C, 77.01; H, 8.31. Found: C, 77.18; H, 8.39.

cis-(±)-[(6-Methyl-3-cyclohexen-1-ylmethyl)sulfinyl]benzene (142). The general procedure of reference 117 was used. Aqueous $NaIO_4$ (0.5 M, 12 mL, 6 mmol) was added to a solution of sulfide **141** (1.08 g, 4.95 mmol) in methanol (50 mL). The mixture was stirred at room temperature overnight, diluted with water (250 mL), and extracted with $CHCl_3$ (3 x 100 mL). The organic extracts were washed with saturated NaCl (100 mL), dried, and concentrated. Flash chromatography of the residue over silica gel (15 x 3 cm, 3:1 hexane-ethyl acetate) afforded sulfoxide **142** (1.09 g, 4.65 mmol, 94%) as an apparently homogeneous (TLC; silica, 3:1 hexane-ethyl acetate) oil which partially solidified on standing: NMR ($CDCl_3$, 200 MHz) showed two diastereoisomers in approximately equal proportions. δ 7.71-7.60 (m, 2H), 7.60-7.44 (m, 3H), 5.72-5.56 (m, 2H), 2.90-2.48 (m, 2H), 2.48-1.56 (m, 6H), 0.88 (2 overlapping doublets, J = 7 Hz, 3H); ^{13}C NMR ($CDCl_3$, 22.6 MHz) δ 131.0, 130.9, 129.2, 126.2, 125.8, 124.7, 124.4, 124.1, 123.9, 60.7, 60.5, 32.4, 31.9, 31.6, 30.8, 29.5, 29.0, 28.4, 15.9, 14.8; IR (film) 1650 cm^{-1}; exact mass, m/e 234.1077 (calcd for $C_{14}H_{18}OS$, m/e 234.1078). Anal. Calcd for $C_{14}H_{18}OS$: C, 71.75; H, 7.74; O, 6.83. Found: C, 71.86; H, 7.76; O, 6.56.

cis-(±)-6-Methyl-γ-phenylsulfinyl-3-cyclohexene-1-propanol (143). A solution of *n*-butyllithium (1.71 M, 0.64 mL, 1.09 mmol) in hexane was added dropwise to a stirred, ice cooled solution of sulfoxide **142** (231 mg, 0.985 mmol) in dry THF (4 mL). After 20 min, ethylene oxide (*ca.* 5 mL, 4.4 g, 0.1 mol) was introduced via a transfer needle, by evaporation from an adjacent flask. After all of the ethylene oxide had distilled over, the reaction mixture was poured into saturated NH_4Cl (20 mL) and extracted with $CHCl_3$ (3 x 20 mL). The organic solution was dried and concentrated. Flash chromatography of the residue over silica gel (15 x 2 cm, 3:1 hexane-ethyl acetate, then 1:1 hexane-ethyl acetate, then pure ethyl acetate) gave unreacted sulfoxide **142** (30.9 mg, 0.132 mmol, 13%) and alcohol **143** (151 mg, 0.543 mmol, 55% (64% based on recovered starting material)) as an oily solid. Compound **143** was a partially resolvable (TLC, silica, ethyl acetate) mixture of diastereoisomers: NMR ($CDCl_3$, 200 MHz) showed the presence of four isomers. δ 7.55 (m, 5H), 5.81-5.52 (m, 2H), 4.42 and 4.25 (br s, 0.5 H), 3.81 (m, 0.5H), 3.65-3.32 (m, 1.5H), 3.14 (m, 0.5H), 2.91-1.42 (m, 9H), 1.10-0.84 (4 overlapping doublets, 3H); IR (CCl_4) 3320, 1655 cm^{-1}; exact mass, m/e 278.1338 (calcd for $C_{16}H_{22}O_2S$, m/e 278.1340). Anal. Calcd for $C_{16}H_{22}O_2S$: C, 69.03; H, 7.96; S, 11.52. Found: C, 68.09; H, 8.08; S, 11.32.

cis-(±)-6-Methyl-3-cyclohexene-1-propanol (144). Ethylamine (*ca.* 5 mL, 3.4 g, 0.08 mol) was distilled from lithium into a solution of sulfoxide alcohol **143** (142 mg, 0.510 mmol) in dry THF (5 mL), cooled to -78°C. Lithium (*ca.* 18 mg, 2.6 mmol) was added and the mixture was stirred at -78°C for 1 h and at 0°C for 5 h. Excess lithium was removed and the reaction mixture was poured into saturated NH_4Cl (10 mL). The layers were separated and the aqueous phase was extracted with ether (3 x 15 mL). The combined organic extracts were dried and concentrated. Flash chromatography of the residue over silica gel (15 x 1 cm, 3:1 hexane-ethyl acetate) and Kugelrohr distillation (90°C, 0.3 mm) gave alcohol **144** (56.8 mg, 0.368 mmol, 72%) as a clear, colourless, homogeneous (TLC, silica, 3:1 hexane-ethyl acetate) oil of greater than 98% purity (VPC; QF1, 150°C): NMR ($CDCl_3$, 200 MHz) δ 5.61 (m, 2H), 3.68 (t, J = 6 Hz, 2H), 3.43-1.07 (m, 11H), 0.89 (d, J = 7 Hz, 3H); ^{13}C NMR ($CDCl_3$, 50.32 MHz) δ 125.7 (d), 125.5 (d), 63.3 (t), 36.6 (d), 32.8 (t), 30.8 (t), 30.0 (d), 28.4 (t), 27.8 (t), 14.1 (q); IR (film) 3630, 3580-3140, 1650 cm^{-1}; exact

mass, m/e 154.1361 (calcd for $C_{10}H_{18}O$, m/e 154.1358). Anal. Calcd for $C_{10}H_{18}O$: C, 77.87; H, 11.76. Found: C, 77.92; H, 11.56.

***cis*-(±)-[(6-Methyl-3-cyclohexen-1-ylmethyl)sulfonyl]benzene (145).** Aqueous $NaIO_4$ (0.5 M, 16 mL, 8 mmol) was added to a solution of sulfoxide **142** (499 mg, 2.13 mmol) in methanol (25 mL). The mixture was stirred at room temperature for 50 h, diluted with water (50 mL) and extracted with $CHCl_3$ (3 x 50 mL). The organic extracts were dried and concentrated. Flash chromatography of the residue over silica gel (15 x 2 cm, 3:1 hexane-ethyl acetate, then 1:1 hexane-ethyl acetate) gave unreacted sulfoxide **142** (70.7 mg, 0.302 mmol, 14%) and sulfone **145** (399 mg, 1.59 mmol, 75% (87% based on recovered starting material)) as an homogeneous (TLC; silica, 3:1 hexane-ethyl acetate) oil: NMR ($CDCl_3$, 200 MHz) δ 7.94-7.80 (m, 2H), 7.69-7.42 (m, 3H), 5.56 (m, 2H), 3.02 (d, J = 6 Hz, 2H), 2.40-1.82 (m, 5H), 1.65 (dm, J = 16 Hz, 1H), 0.83 (d, J = 6.8Hz, 3H); ^{13}C NMR ($CDCl_3$, 50.32 MHz) δ 133.5 (d), 129.2 (d), 127.8 (d), 125.9 (d), 124.5 (d), 57.2 (t), 32.1 (d), 31.2 (t), 30.5 (d), 29.0 (t), 15.7 (q); IR (film) 1650 cm^{-1}; exact mass (no M^+) m/e 108.0939 (calcd for C_8H_{12} ($M-C_6H_6O_2S$), m/e 108.0939). Anal. Calcd for $C_{14}H_{18}O_2S$: C, 67.17; H, 7.25; S, 12.81. Found: C, 67.03; H, 7.11; S, 12.95.

***cis*-(±)-2-(6-Methyl-3-cyclohexen-1-yl)methyl-1,3-dithiane (152).** The general procedure of reference 126 was used. A solution of *n*-butyllithium in hexane (1.71 M, 1.24 mL, 2.12 mmol) was added to a stirred solution of 1,3-dithiane (243 mg, 2.02 mmol) in dry THF (10 mL), cooled to -78°C. The solution was warmed to *ca.* -20°C for 2 h and then a solution of bromide **140** (380 mg, 2.01 mmol) in dry THF (1.0 mL plus 1.0 mL rinse) was added and the mixture was warmed to room temperature. The solution was stirred at room temperature overnight, and was then poured into water (30 mL) and extracted with $CHCl_3$ (3 x 20 mL). The combined organic extracts were washed with 7% KOH (2 x 20 mL) and saturated NaCl (20 mL), dried, and concentrated. Flash chromatography of the residue over silica gel (15 x 2 cm, 49:1 hexane-ethyl acetate) gave an apparently homogeneous (TLC; silica, 19:1 hexane-ethyl acetate) oil. Upon Kugelrohr distillation, however, first a small amount of white solid sublimed (70°C, 0.3 mm) (recovered 1,3-dithiane) followed by dithiane **152** (224 mg, 0.981 mmol, 49%) as a clear, colourless oil of greater than 99%

purity (VPC; QF1, 190°C): NMR ($CDCl_3$, 200 MHz) δ 5.59 (m, 2H), 4.10 (t, J = 7.3, 1H), 3.03-2.75 (m, 4H), 2.34-1.57 (m, 10H), 0.91 (d, J = 6.8 Hz, 3H); ^{13}C NMR ($CDCl_3$, 50.32 MHz) δ 125.6 (d), 125.1 (d), 45.6 (d), 37.1 (t), 33.4 (d), 32.2 (t), 30.5 (t), 30.3 (t), 29.8 (d), 28.3 (t), 26.0 (t), 14.5 (q); IR (film) 1648 cm^{-1}; exact mass, m/e 228.1009 (calcd for $C_{12}H_{20}S_2$, m/e 228.1007). Anal. Calcd for $C_{12}H_{20}S_2$: C, 63.10; H, 8.83. Found: C, 63.52; H, 8.85.

***cis*-(±)-4-(2-Methylsulfinyl-2-methylthio)ethyl-5-methyl-cyclohexene (153).** A solution of *n*-butyllithium in hexane (1.71 M, 2.90 mL, 4.96 mmol) was added to a stirred, ice cooled solution of (methylsulfinyl)(methylthio)methane[129] (616 mg, 4.96 mmol) in dry THF (20 mL). The solution was stirred for 30 min at this temperature and then a solution of bromide **140** (853 mg, 4.51 mmol) in dry THF (1.0 mL plus 1.0 mL rinse) was added, followed by HMPA (1.57 mL, 1.62 g, 9.03 mmol). The solution was stirred for 24 h at room temperature, and was then diluted with water (60 mL) and extracted with $CHCl_3$ (3 x 50 mL). The organic extracts were washed with saturated NaCl (50 mL), dried, and concentrated. Flash chromatography of the residue over silica gel (15 x 3 cm, ethyl acetate, then again, 15 x 2 cm, ethyl acetate) gave compound **153** (663 mg, 2.85 mmol, 63%) as an apparently homogeneous (TLC; silica, ethyl acetate) oil: NMR ($CDCl_3$, 200 MHz) δ 5.58 (m, 2H), 3.61-3.44 (m, 1H), 2.71 and 2.69 (two broad singlets, total integration 2H), 2.56 (s, 1H), 2.45-1.60 (m, containing singlets at δ 2.28, 2.22, 2.18, 2.17, total integration 10H), 1.60-1.32 (m, 1H), 0.96-0.80 (m, 3H); IR (film) 1650 cm^{-1}; exact mass (no M^+), m/e 169.1049 (calcd for $C_{10}H_{17}S$ (M - CH_3OS), m/e 169.1051). Anal. Calcd for $C_{11}H_{20}OS_2$: C, 56.85; H, 8.67; S, 27.59. Found: C, 57.13; H, 8.86; S, 27.71.

***cis*-(±)-6-Methyl-3-cyclohexene-1-acetaldehyde (154).**

a) From Bromide 140.

i) Using Disodium tetracarbonylferrate. The general procedure of reference 122 was used. A solution of triphenylphosphine (205 mg, 0.782 mmol) in dry THF (1.0 mL) and a solution of bromide **140** (124 mg, 0.656 mmol) in THF (1.0 mL plus 1.0 mL rinse) were added to a stirred suspension of $Na_2Fe(CO)_4$ (194 mg, 0.908 mmol) in THF (5.0 mL). The mixture as stirred at room temperature for 3 h and then glacial acetic acid (0.50 mL,

0.52 g, 8.7 mmol) was added, followed by ether (25 mL), and water (10 mL). The layers were separated, dried, and concentrated to afford a red semi-solid. This was taken up in ether (50 mL) and filtered through a pad of Florisil (*ca.* 8 x 2.5 cm), which was then washed with ether (*ca.* 100 mL). The green filtrate was concentrated to afford a green semi-solid. Flash chromatography of this material over silica gel (15 x 1 cm, 9:1 hexane-ethyl acetate) gave some impure fractions containing aldehyde **154** and a yellow compound having the same Rf (TLC, silica, 9:1 hexane-ethyl acetate). NMR ($CDCl_3$, 80 MHz) showed the desired aldehyde; however the signals were considerably broadened.

ii) Using a Polymer Supported Iron Carbonyl Complex. The general procedure of reference 123 was used: Amberlyst A-26 (hydroxide form) (60 g) was stirred with aqueous HCl (1 M, 1 L) for 3 days. The resin was filtered off and washed with distilled water until the filtrate was neutral (pH paper). The resin was washed with degassed water, methanol, and ether, and was then dried under vacuum (0.3mm, 60°C) for 4 h.

Pentacarbonyliron (1.15 mL, 1.71 g, 8.75 mmol) was added to a stirred solution of KOH (1.4 g, 25.0 mmol) in 1:1 ethanol-water (25 mL) and the resulting solution was heated at reflux for 2 h. The solution was cooled to room temperature and the previously prepared resin (6 g) was added. After being stirred for 15 min, the resin was filtered off under argon, washed with degassed water, methanol, and ether, and dried by a stream of argon.

A solution of bromide **140** (409 mg, 2.16 mmol) in dry THF (1.0 mL plus 1.0 mL rinse) was added to a suspension of the polymer supported iron reagent in dry THF (15 mL) and the mixture was heated at reflux overnight. The mixture was cooled to room temperature, diluted with ether (25 mL), and filtered through a pad of Celite (2 x 2.5 cm), which as then washed with ether (*ca.* 100 mL). The filtrate was concentrated and flash chromatography of the residue over silica gel (15 x 2 cm, 9:1 hexane-ethyl acetate) afforded aldehyde **154** (85.7 mg, 0.620 mmol, 29%) as a slightly impure (containing a yellow, UV active impurity having the same Rf (TLC; silica, 9:1 hexane-ethyl acetate)) oil.

b) From Dithiane 152.

i) Using Mercury (II) Hydrolysis. The general procedure of reference 126 was used: A solution of dithiane **152** (210 mg, 0.920 mmol) in THF (0.5 mL) was added to a stirred mixture of red mercury (II) oxide (525 mg, 2.48 mmol) and boron trifluoride

etherate (0.25 mL, 0.29 g, 2.0 mmol) in 15% aqueous THF (4.0 mL). The mixture was stirred at room temperature for 1.5 h and was then diluted with ether (10 mL) and filtered through a pad of Celite (1 x 2.5 cm), which was washed with ether (15 mL). The combined ether solutions were washed with saturated Na_2CO_3 (2 x 15 mL) and saturated NaCl (2 x 15 mL), dried, and concentrated by atmospheric pressure distillation of the solvent. Flash chromatography of the residue over silica gel (15 x 1 cm, 19:1 hexane-ethyl acetate) and concentration of pure product fractions by atmospheric pressure distillation of the solvent, gave aldehyde **154** (149 mg, 0.355 mmol, 39%) as an homogeneous (TLC; silica, 19:1 hexane-ethyl acetate) oil.

ii) Using Copper (II) Hydrolysis. The general procedure of reference 127 was used. A mixture of dithiane **152** (229 mg, 1.00 mmol), $CuCl_2$ (272 mg, 2.02 mmol) and CuO (321 mg, 4.03 mmol) in aqueous 99% acetone (10 mL) was heated at reflux for 2 h and was then cooled to room temperature and filtered through a pad of Celite (1 x 2.5 cm) which was washed with acetone (10 mL). The filtrate was concentrated and the residue was triturated with ether (25 mL). The ether solution was filtered through a pad of Celite (1 x 2.5 cm), which was then washed with ether (*ca.* 25 mL). The filtrate was dried, and concentrated. Flash chromatography of the residue over silica gel (15 x 1 cm, 19:1 hexane-ethyl acetate) gave aldehyde **154** (23.0 mg, 0.166 mmol, 17%) as an homogeneous (TLC; silica, 9:1 hexane-ethyl acetate) oil.

c) From Compound 153. Aqueous 70% $HClO_4$ (3 drops) was added to a solution of compound **153** (166 mg, 0.713 mmol) in 15% aqueous THF (4 mL), cooled to 0°C. After 30 min, the solution was warmed to room temperature and more 70% $HClO_4$ (5 drops) was added. After 1 h, and again after 3 h, additional portions of 70% $HClO_4$ (10 drops) were added. After a further 2 h period (5.5 h total, 28 drops of 70% $HClO_4$ total), the reaction appeared complete (TLC; silica 9:1 hexane-ethyl acetate) and so the mixture was diluted with ether (40 mL) washed with saturated Na_2CO_3 (20 mL) and water (20 mL). The combined aqueous solutions were extracted with ether (20 mL) and the combined ether solutions were dried and concentrated by atmospheric pressure distillation of the solvent. Flash chromatography of the residue over silica gel (15 x 1 cm, 1:1 hexane-ethyl acetate) and concentration of pure product fractions by atmospheric pressure distillation, afforded aldehyde **154** (80.2 mg, 0.580 mmol, 81%) as an apparently homogeneous (TLC;

silica, 9:1 hexane-ethyl acetate) oil of greater than 95% purity (VPC; QF1, 150°C).* NMR ($CDCl_3$, 200 MHz) δ 9.80 (t, J = 1.9 H, 1H), 5.60 (m, 2H), 2.52-2.00 (m, 5H), 2.00-1.63 (m, 3H), 0.88 (d, J = 6.8 Hz, 3H); ^{13}C NMR ($CDCl_3$, 50.32 MHz) δ 202.6, 125.8, 124.8, 45.1, 31.7, 31.5, 30.3, 29.1, 15.7; IR (film); 1720, 1648 cm^{-1}; exact mass, m/e 138.1042 (calcd for $C_9H_{14}O$, m/e 138.1045).

(3*R*)-7-[(1*R,*S**,6*R**,*S**)-6-Methyl-3-cyclohexen-1-yl]-1-(phenylmethoxy)-5-hepten-3-ol (155)**. The general procedure of reference 120 was used, with some modifications. A solution of *sec*-butyllithium in hexane (1.00 M, 2.0 mL, 2.0 mmol) was added to a suspension of methyltriphenylphosphonium bromide (356 mg, 1.00 mmol) in dry ether (10 mL), cooled to -78°C. The suspension was stirred at this temperature for 30 min, then at room temperature for 3.5 h. Epoxide **74** (161 mg, 0.904 mmol) in ether (1.0 mL plus 1.0 mL rinse) was added and the suspension was stirred at room temperature for 5 h. Aldehyde **154** (103 mg, 0.744 mmol) in ether (1.0 mL plus 1.0 mL rinse) was added and the mixture was stirred at room temperature overnight. The reaction mixture was then poured into water (20 mL), the layers were separated and the aqueous phase was extracted with dichloromethane (2 x 15 mL). The combined organic solutions were dried and concentrated. Flash chromatography of the residue over silica gel (15 x 1 cm, 9:1 hexane-ethyl acetate) afforded compound **155** (61.0 mg, 0.194 mol, 26%) as an apparently homogeneous (TLC; silica, 3:1 hexane-ethyl acetate) oil. Spectroscopic analysis, however, indicated a mixture of diastereoisomers: NMR ($CDCl_3$, 200 MHz) δ 7.32 (m, 5H), 5.57 (br s, 2H), 5.45 (m, 2H), 4.51 (s, 2H), 3.81 (m, 1H), 3.76-3.54 (m, 2H), 2.88 (br s, 0.3H), 2.78 (br s, 0.7H), 2.33-1.52 (m, 12H), 0.92-0.77 (m, incorporating a doublet at δ 0.85, J = 6.8 H, total integration 3H); ^{13}C NMR ($CDCl_3$, 200 MHz) showed two sets of signals which could be separated on the basis of peak height. The major isomer had δ 138.0, 132.8, 128.4, 127.6, 126.9, 125.7, 125.5, 73.2, 70.4, 68.8, 40.8, 37.0, 35.9, 34.8, 32.6, 29.8, 28.2, 14.3. The minor isomer had** δ 131.6, 71.0, 69.0, 37.3, 35.4, 28.3; IR (CCl_4) 3535, 1650 cm^{-1}; exact mass, m/e 314.2251 (calcd for $C_{21}H_{30}O_2$, m/e 314.2246). Anal. Calcd for $C_{21}H_{30}O_2$: C, 80.21; H, 9.62. Found: C,

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*This compound underwent considerable decomposition upon Kugelrohr distillation (120°C, 20 mm).
**Not all of the signals for the minor isomer were clearly resolved.

80.29: H. 9.76.

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